Dissertation on

"ASSESSMENT OF PLATELETS IN PATIENTS WITH PULMONARY HYPERTENSION"

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CERTIFICATE

This is to certify that the dissertation entitled "**ASSESSMENT OF PLATELETS IN PATIENTS WITH PULMONARY HYPERTENSION"** is a bonafide original work done by **Dr.GOVARDHINI.V**, in partial fulfillment of the requirements for M.D. GENERAL MEDICINE BRANCH – I examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2016, under our supervision and guidance.

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DECLARATION

I hereby solemnly declare that the dissertation entitled“ **ASSESSMENT OF PLATELETS IN PATIENTS WITH PULMONARY HYPERTENSION”** is done by me at Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai during 2015 under the guidance and supervision of **Prof.Dr.P.VIJAYARAGHAVAN, M.D.,** This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai towards the partial fulfillment of requirement for the award of M.D. Degree in General Medicine (Branch I)

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CONTENTS

INTRODUCTION

INTRODUCTION

Pulmonary circulation is a low resistance, high compliance vascular bed and Only organ to receive entire cardiac output (CO). Changes in CO as well as pleural/alveolar pressure affect pulmonary blood flow and there by affect the resistance offered by the pulmonary vasculature[1].

Pulmonary hypertension is defined as a condition associated with elevation of mPAP > 25 mm Hg at rest. It has multifactorial pathogenesis with various aetiologies grouped under five categories[2]. They are classified according to the pathogenic mechanisms involved. Differentiation into groups is important as the treatment is given according to the group of pulmonary hypertension[3]. Its causes significant Morbidity and mortality among the affected individuals and hence earlier diagnosis and treatment is aimed.

Currently haematological issues has been identified to be associated with the pathogenesis and progression of disease, especially with platelets and its activation resulting in initiation and progression of disease. The role of platelets has been studied extensively and found to be associated with idiopathic pulmonary hypertension . Platelets has been found to be linked in almost all causes pulmonary hypertension and the

mean platelet volume has been found to be increased in all causes of pulmonary hypertension.

Thrombocytopenia has been identified as a independent predictor of mortality among patients with pulmonary hypertension[4]. Even though the association of platelets in all groups of pulmonary hypertension is undoubted, its relation to the severity of pulmonary hypertension and effect of treatment for pulmonary hypertension on the platelet indices are lacking.

Whether platelet indices could be used as a simple surrogate marker of severity of hypertension in rural population there by can be used to refer patients for higher centres for further evaluation and early diagnosis of pulmonary hypertension.

Hence in this study we aimed to bring out the platelet morphology, count, function and activation using platelet indices as surrogate markers in patients with pulmonary hypertension. Its correlation assessed with severity of pulmonary hypertension. And also the effect of treatment of pulmonary hypertension.

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

1. To study the prevalence of various groups of pulmonary hypertension among patients attending Rajiv Gandhi government general hospital.

2. To access the severity of pulmonary hypertension using echocardiogram among patients with pulmonary hypertension.

3. To study the platelet morphology, platelet indices and platelet function in various groups of pulmonary hypertension.

4. To study the relationship of platelet indices to the mean pulmonary artery pressure and severity of pulmonary hypertension.

5. To study the relationship of platelet function with mean pulmonary artery pressure and severity of pulmonary hypertension.

6. To study the effect of treatment on severity of pulmonary hypertension and its impact of the platelet indices.

REVIEW

OF

LITERATURE

HISTORY OF PULMONARY HYPERTENSION

First identified and reported by Ernst Von Romberg in the year 1891 as pulmonary arterial sclerosis. In 1935 Brenner gave the anatomic description. The name primary pulmonary hypertension has been coined in 1951 by David Dresdale a research fellow of Cournand and Richards. He also studies the hemodynamic variables in pulmonary hypertension. In 1958 Heath and Edwards defined the changes in spectrum of congenital heart disease and Eisenmenger syndrome described[5]. Initial classification by Edward and Heath in 1958, was a pathological classification, dividing into 6 progressive grades starting from persistence of foetal pulmonary vasculature to necrotising arteritis.

Since then a lot of research and discussion were held by WHO conferences and updated and incorporated newer classifications of pulmonary hypertension. After the year 2000 with the diagnosis of genetic background for heritable cause of pulmonary hypertension namely BMPR2 a lot of newer genes begin to be investigated to be associated with pulmonary hypertension even in sporadic cases. With the updates, the classification of pulmonary hypertension according to the aetiology has gone through lot of frequent changes and in Dana Point classification in 2008, pulmonary hypertension is classified into 5 groups. The latest classification was given in 2013, conference held at France.

REVIEW OF LITERATURE

DEFINITION:

Pulmonary hypertension previously called an orphan disease is defined as elevation of mean pulmonary artery pressure (mPAP) of 25mmHg or greater at rest measured by right heart catheterisation[6] (RHC). This elevation in the pulmonary artery pressure is due to end result of diverse diseases. When no cause for the pulmonary hypertension could be found, the term Primary Pulmonary Hypertension was used. When the cause could be identified, it is called as Secondary Pulmonary Hypertension.

From mid 20th century, lot of research and development of RHC techniques by National Institute of Health, NIH, primary Pulmonary Registry and by various conferences concluded the clear guidelines for classification of Pulmonary Hypertension subcategories.

PULMONARY VASCULATURE:

Pulmonary and Bronchial arteries are the arterial supply to the lungs whereas pulmonary and azygous vein form the venous drainage channels. Each pulmonary artery usually accompanies the corresponding generation of bronchus and divides till the respiratory bronchioles.

Pulmonary artery consists of a layer of endothelial cells with basement membrane. Adventitia consists of fibrous tissue which is in contact with the fibrous connective tissue of the peribronchial region. In the media, the pulmonary vasculature has both elastic and muscular component[7]. At its origin, it is more of elastic component which is highly distensible for minimal pressure. As the vessel divides and decreases in size, it becomes more muscular, about 500 microns in diameter with less elastic lamina, thereby less distensible for the same amount of pressure.

Once the pulmonary arteries divide into arterioles, which is about 100 microns in diameter, it consists of single layer of endothelium covered by thin layer of elastic lamina which then give rise to capillaries. Capillaries are formed as only a layer of endothelium attached to basement membrane. This network of capillaries are attached to the wall of the alveolus. In the periphery of the alveolus, the venules originate which ultimately into the main veins[8].

Bronchial artery gives nutrition to airways by ramifying into capillary network and drain both into pulmonary veins and systemic venous bed. Since it also drain into the pulmonary vein, which carries the oxygenated blood, it forms a trivial physiological right to left shunt.

CIRCULATION GANONG 23RD

PULMONARY CIRCULATION	BRONCHIAL CIRCULATION
• LOW-PRESSURE, HIGH-FLOW CIRCULATION	HIGH-PRESSURE, LOW-FLOW CIRCULATION
CONTAIN 100% CARDIAC OUTPUT	CONTAIN 1-3% CARDIAC OUTPUT
SUPPLIES RESPITARY BRONCHIOLS TO ALVEOLI	SUPPLIES BRONCHI TO TERMINAL BRONCHIOLS
ARIES FROM HEART	ARIES FROM AROTA
EXCEPTION ARTERY CARRY DEOXYGENETED BLOOD	SHUNT(COMMON)

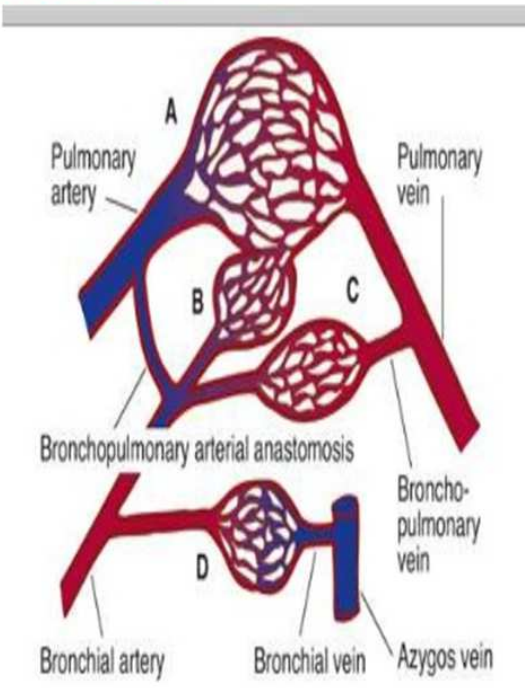


Figure 1. Pulmonary Circulation

HEMODYNAMICS OF PULMONARY CIRCULATION

The normal pulmonary circulation has a high flow, low pressure and low resistance. Normal pulmonary vascular bed offers 10 % less resistance as compared to systemic bed. Normal mPAP at rest is 14± 3.3 mmHg. It is independent of age and ethinicity. Pulmonary hypertension is classified as precapillary and post capillary based on Pulmonary Artery Wedge Pressure (PAWP)[9]. If PAWP is 15mmHg or less, it is precapillary and 15mmHg or more it is post capillary. Some individuals has elevated

mPAP, PAWP and transpulmonary gradient {mPAP- PAWP} greater than 12 mmhg showing a mixed picture

Definition	Characteristics	Clinical group(s)
Pulmonary hypertension	Mean PAP ≥ 25mmHg	All
Pre-capillary PH	Mean PAP ≥ 25mmHg PWP ≤ 15mmHg CO normal or reduced	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial
Post-capillary PH Passive Reactive	Mean PAP ≥ 25mmHg PWP > 15mmHg CO normal or reduced TPG ≤ 12mmHg TPG > 12mmHg ☒	2. PH due to left heart disease

Figure 2. Definition of Pulmonary Hypertension Types

The Pulmonary Vascular Resistance (PVR) and Total Pulmonary resistance (TPR) are important in the hemodynamics and they are calculated as ratios:

PVR = (mPAP – PAWP)/CO

TPR = mPAP/CO

The ratios are expressed as mmhg/liter/min, called as a wood unit.

With exercises, mPAP increases but is dependent on level of exercise and age. Mild exercise in younger individuals increases mPAP around 4.8mmhg where as 8.4 mmhg in individuals more than 50 years. Hence it becomes difficult to arrive at normal mPAP during exercise. There is not enough studies to define it. So the concept of exercise

induced Pulmonary Hypertension was abandoned. PVR and TPR and the impact of it on exercise, age and posture have been discussed. With exercise, the cardiac output increases thereby TPR and PVR decreases. For a 85% increase in cardiac output, there is 25% decrease in TPR and 12% decrease in PVR. As the age increases, there is no significant difference, instead the TPR may increase by 17% and PVR remains unchanged.

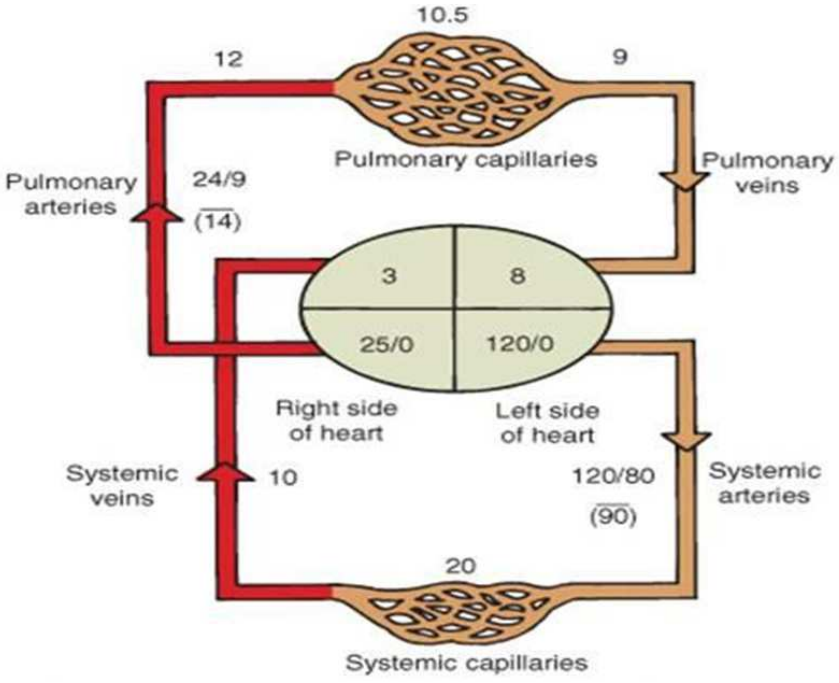


Figure 3. Haemodynamics.

PATHOPHYSIOLOGY:

Pulmonary hypertension develops by diverse mechanisms which ultimately results in elevation of mPAP. After many studies it has been postulated that it is mainly due to the imbalance between vasodilatation

and vasoconstriction mechanisms, thrombosis and remodelling of pulmonary arterial walls. Remodelling of pulmonary vasculature occurs in all layers of pulmonary arteries with diameter less than 500 micro meter and inflammatory cells. Significant role is played by platelets[10].

Early in pathogenesis is vasoconstriction of pulmonary vasculature due endothelial dysfunction and abnormal expression of potassium channels. Endothelial dysfunction results in decreased production vasodilators (nitric oxide and prostacyclin) and increased production of endothelin-1 like vasoconstrictors[11]. These abnormalities results in increased vascular tone and promotes remodelling. Other mediators involved are bone morphogenetic proteins (BMP), sertonin, angiopoeitin and growth factors mainly transforming growth factor –beta superfamily

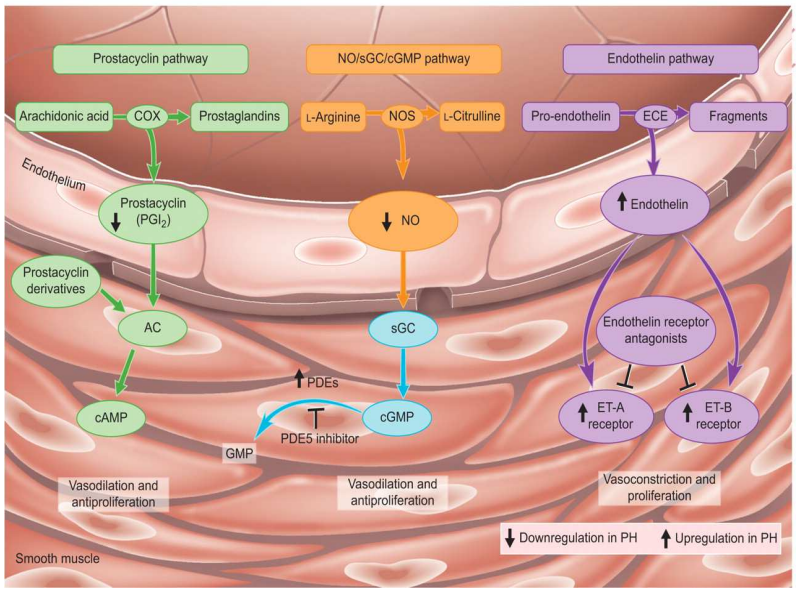
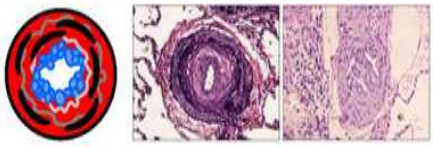


Figure 4. Pathophysiology

HISTOPATHOLOGY:

Histopathology differs in different groups of pulmonary hypertension.

Clinical Classification Group	Characteristics of arteriopathy	Histological examples
1. Pulmonary arterial hypertension 'Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis	• Medial hypertrophy • Muscularization of arterioles • Cellular proliferation of intima layer • Concentric laminar intimal fibrosis • Plexiform lesions • Fibrinoid necrosis	
2. PH due to left heart disease	• Medial hypertrophy • Muscularization of arterioles and veins • non-obstructive intimal fibrosis • moderate intima fibrosis veins	
3. PH due to lung disease or hypoxia	• Large arteries mostly normal • Medial hypertrophy • Muscularization of arterioles • similar changes to lesser extent in small pulmonary veins	
4. Chronic Thromboembolic PH (CTEPH)	• Mild medial hypertrophy • Eccentric intimal fibrosis • Recanalization of lumen • recent thrombi rare	
5. PH with unclear multifactorial mechanisms	• Muscularization of arterioles and veins (fibrotic lung disease, tumors) • non-obstructive intimal fibrosis (fibrotic lung disease, tumors) • vascular granulomas (sarcoidosis, tuberculosis) • enlargement of bronchial arteries (bronchiectasis)	

Adapted from Wagenvoort and Mooi

Figure 4. Histopathology

Pulmonary Arterial Hypertension:

Small pulmonary arteries less than 500 micrometre showing intimal fibrosis, medial hypertrophy, obliteration with thrombotic lesions, adventitial proliferation and perivascular infiltration by inflammatory cells and complex lesions namely plexiform lesion.[12.] Even though

plexiform lesions are not characteristic of PAH they are a form of neoplastic growth symbolizing dysregulated endothelial growth. They are found in around 90% of cases.

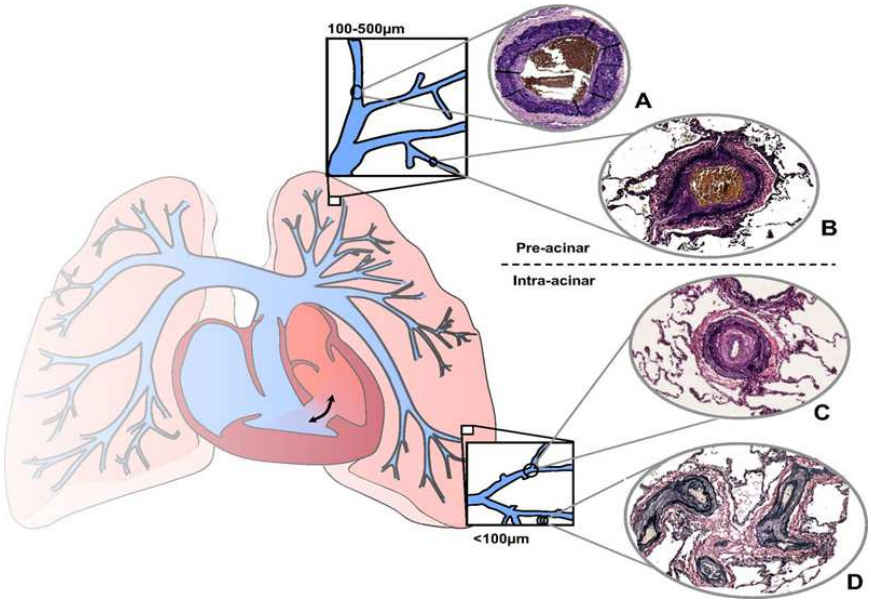
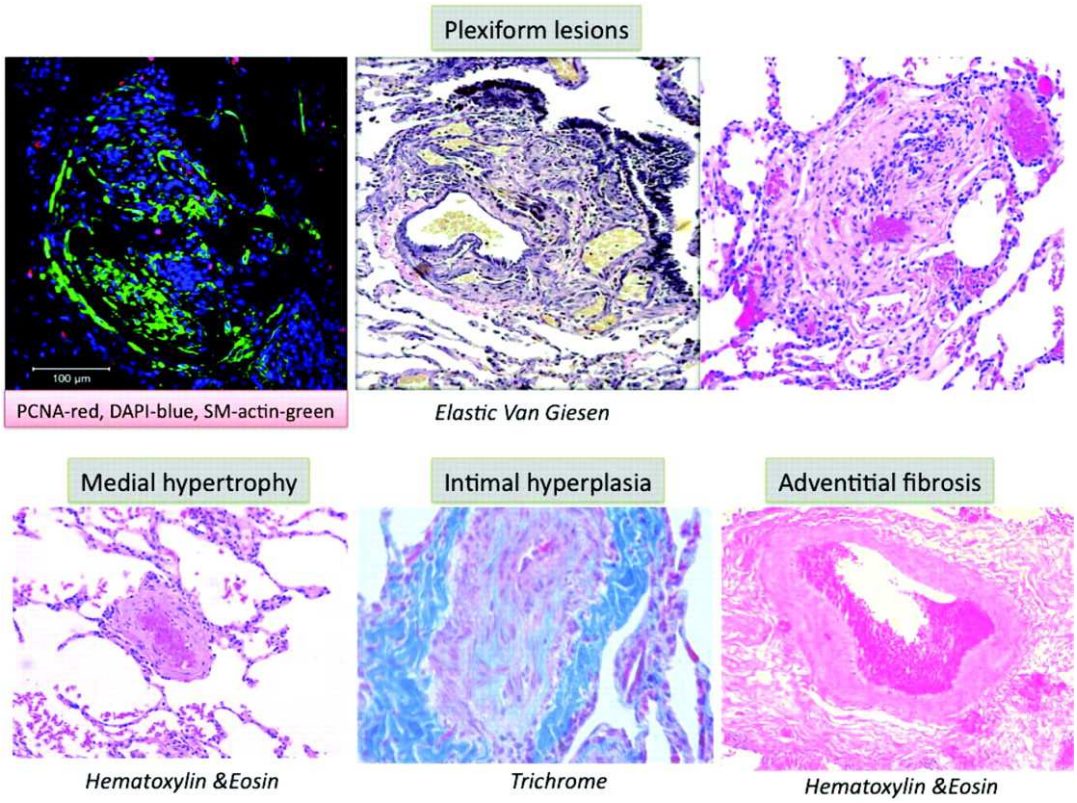


Figure 6. Changes in Pulmonary Vasculature

Plexiform lesions are like a renal glomerulus with central endothelial cells having p27/kip-1 negative and positive cells found in peripheral areas. They produce factor 8 vimentin, type 3 nitric acid synthase and VEGF receptor Pulmonary veins are free from characteristic changes. Presence of plexiform lesions is more specific for pulmonary arterial hypertension.



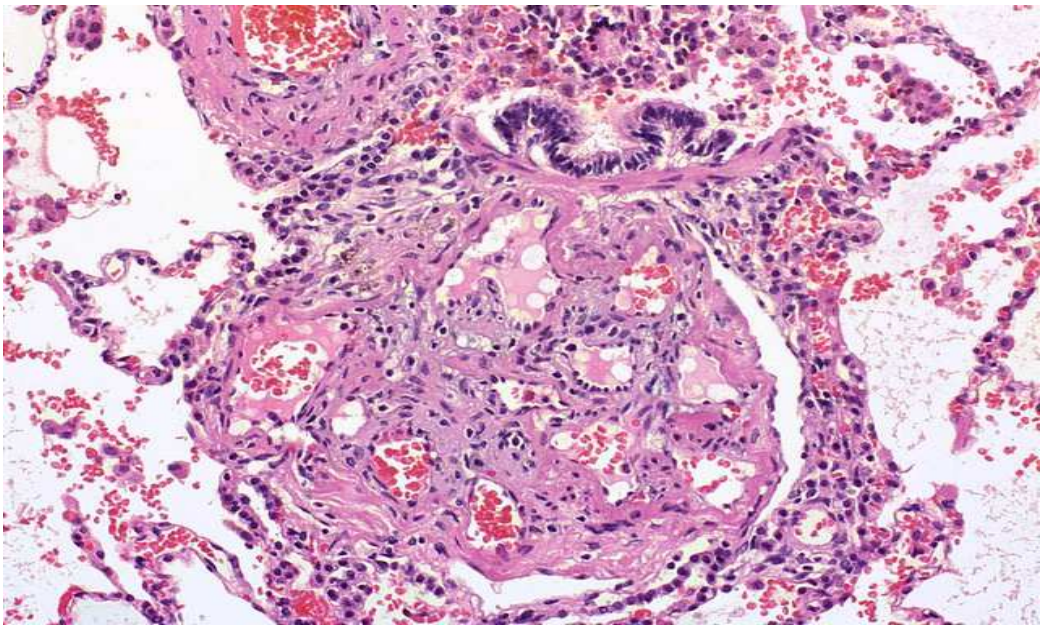


Figure 5. Plexiform Histopathology

PH Due To Left Sided Heart Disease:

Pulmonary veins shows thickening and capillary dilatation , alveolar haemorrhage and interstitial edema. Pulmonary artery may be affected but not with pathognomonic lesion.

PH Due To Lung Diseases:

Destruction of pulmonary artery with emphysematous or fibrotic areas along with other changes like medial hypertrophy and obstruction due to proliferation[13].

PH due to CTEPH:

Thrombus are the important characteristic finding. Could be of various sizes resulting in minimal to total occlusion of pulmonary arteries. Collaterals from nearby arteries namely bronchial, costal, coronary arteries develop to perfuse the totally occluded areas.

PH Due To Multifactorial Mechanisms:

The pathology is heterogeneous as the causes are heterogeneous and they develop due to multifactorial mechanisms.

CLASSIFICATION PULMONARY HYPERTENSION

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, **SMAD9 , CAV1 , KCNK3**
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1''. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart in flow/out flow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Haematologic disorders: **chronic haemolytic anaemia** , myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

* 5th World Symposium on Pulmonary Hypertension, Nice 2013. Main modifications to the previous Dana Point classification are in bold.

Key: BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension

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GROUP.1 PULMONARY ARTERY HYPERTENSION:

They include group of diseases causing a sustained increase of mPAP more than 25 mmhg during rest while PCWP or left atrial pressure or the left ventricle end diastolic pressure less than 15 mmhg. In addition the transpulmonary gradient and the PVR is also increased[14].

Epidemiology:

Rare disease with prevalence of 15 to 20 cases seen per million population.

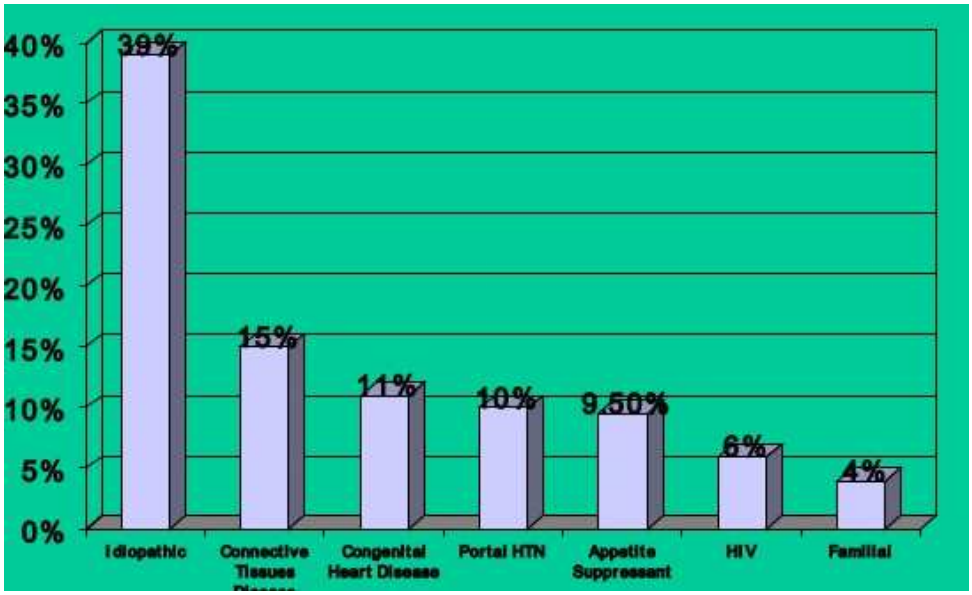


Figure 6. Epidemiology of PAH

Most common cause of pulmonary arterial hypertension is idiopathic followed by CTD. Inherited PAH has the least incidence of 4%.

Idiopathic pulmonary arterial hypertension:

Previously known as primary pulmonary hypertension where the cause of the elevation of mPAP could not be identified. It is the most common type among PAH[15]. Patients were found to be sporadic without family history or risk factor. Females are commaly affected with mean age at presentation being 37 years.

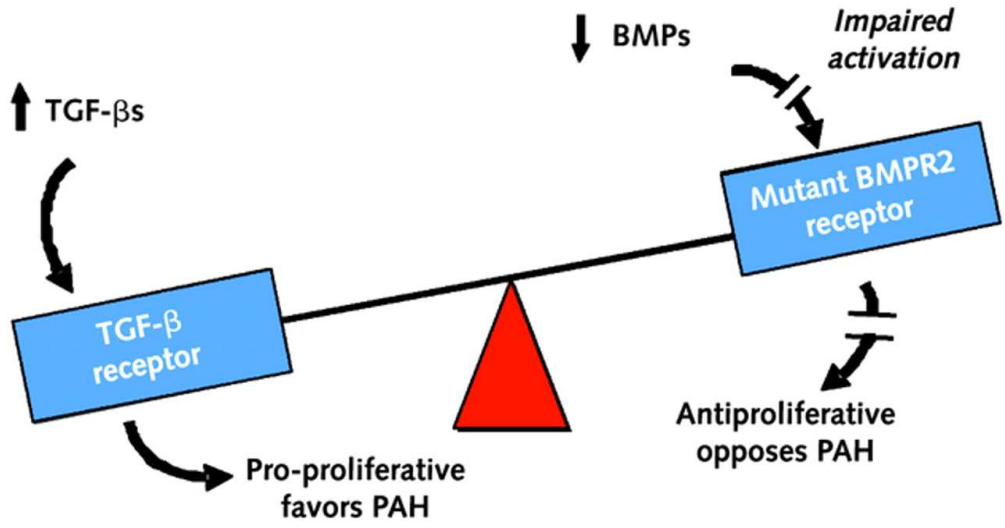
Heritable pulmonary arterial hypertension:

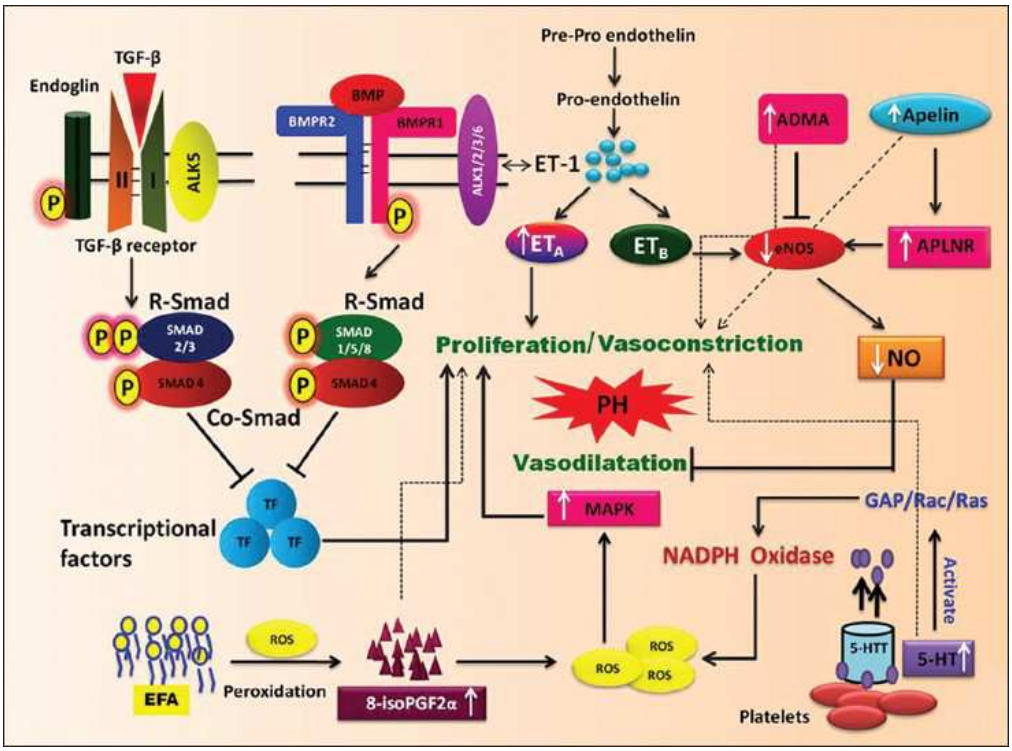
The first case of heritable PAH was diagnosed by Dresdale and his colleagues in 1954. Since then many cases have been reported and lot of research has been done on genetic analysis of affected individuals to bring out the genes involved. It's a autosomal dominant triat with incomplete penetrance showing the phenomenon of anticipation[16].

The most studied is the bone morphogenic protein receptor 2 (BMPR2) belonging to the TGF-beta receptor family and it's the first identified predisposing gene. It is present in chromosome 2 long arm (2q31-32)[17]. It is said to be responsible for the pulmonary endothelial and smooth muscle cell growth and differentiation. The gene is detected in 70 to 80%of cases with family history and 15 to 20% of sporadic cases. Females are commonly affected. Patients with this mutation are younger in age at diagnosis with aggressive course and carry poor prognosis.

Other genes that are involved are activin a receptor type II like kinase 1(ALK-1), endoglin,SMAD-9,CAV1- involved in TGF- beta signaling pathway[18,19].

Figure 7. Genetics in PAH





Drug and toxin induced PAH:

With an epidemic outbreak IPAH due to Aminorex fumarate in 1960, many structurally linked compunds like fenfluramine , dexfenfluramine used as anorexigens were found to be causing PAH and hence withdrawn from market. Some methamphetamines, l-tryptophan, rapeseed oil were found to cause PAH. Dasatinib a tyrosine kinase inhibitor was also found to cause PAH[20].

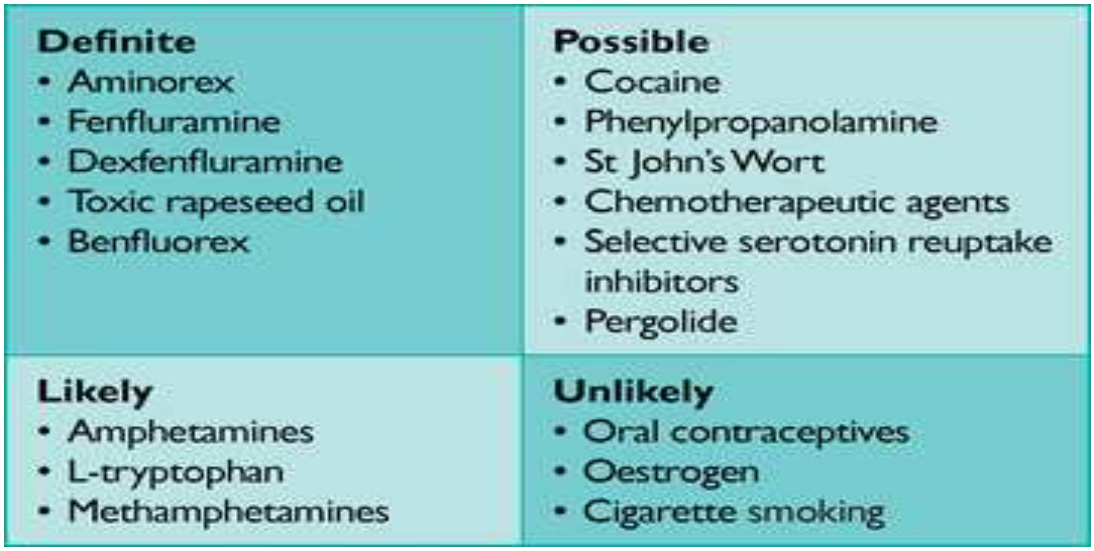


Figure 8. Drugs Causing PAH

Connective tissue disease and PAH:

Associated has been strong with scleroderma spectrum of diseases with the prevalence of 8 to 12%. Patients have a poor prognosis with treatment when compared to other causes of PAH[21]. The high risk patients could be identified with reduction in carbon monoxide diffusion

capacity and echocardiogram screening so as to subject for earlier treatment.

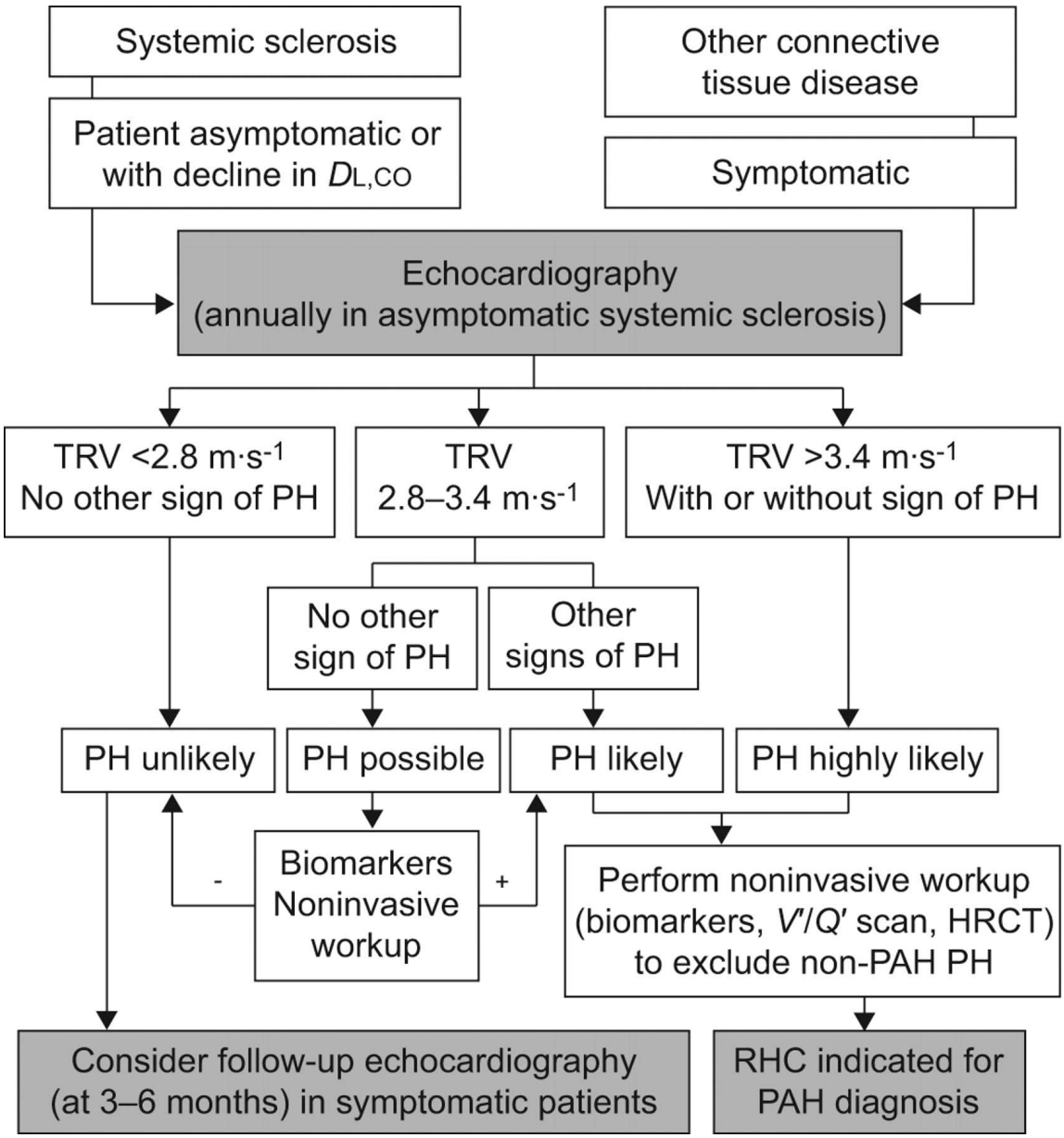


Figure 9. Screening for PAH in CTD

PAH associated with HIV :

Rare disease with incidence of 0.5% not being changed with extensive use of antiretroviral therapy not associated with the CD4+ cell count or the presence of opportunistic infections[22,23]. The mechanism being not known but association with HIV is clearly established. Hence should be suspected in HIV infected patients where any other cause could not be identified.

PAH associated with portal hypertension:

Portopulmonary hypertension(POPH) is the term used when PAH develops in patients with portal hypertension. There is no association with the severity of liver disease or the portal hypertension with the presence or severity of PAH. Seen also in patients with non hepatic causes of portal hypertension. . The prevalence is 2 to 6% and it increases the perioperative risk in patients undergoing liver transplantation[24]

Variable	Normal	Mild	Moderate	Severe
NYHA class	—	I-II	II-III	II-IV
mPAP (mmHg)	15-24	25-34	35-44	>45
CI (L/min/m^2)	2.5-4	>2.5	>2.5	<2.0
PVR (dynes/s/cm^5)	<80	240-500	500-800	>800
RAP (mmHg)	0-5	0-5	5-10	>10
Prognosis	—	Favorable	Questionable	Poor
Specific therapy	—	No	Questionable	Yes
Reversibility after LT	—	Yes	Questionable	No

NYHA = New York heart association, mPAP = Mean pulmonary arterial pressure, CI = Cardiac index, PVR = Pulmonary vascular resistance, RAP = Right atrial pressure, LT = Liver transplantation

It should be differentiated from hepatopulmonary syndrome which is due to vasodilatation that occurs in pulmonary vasculature causing intrapulmonary shunting resulting in hypoxemia and dyspnoea

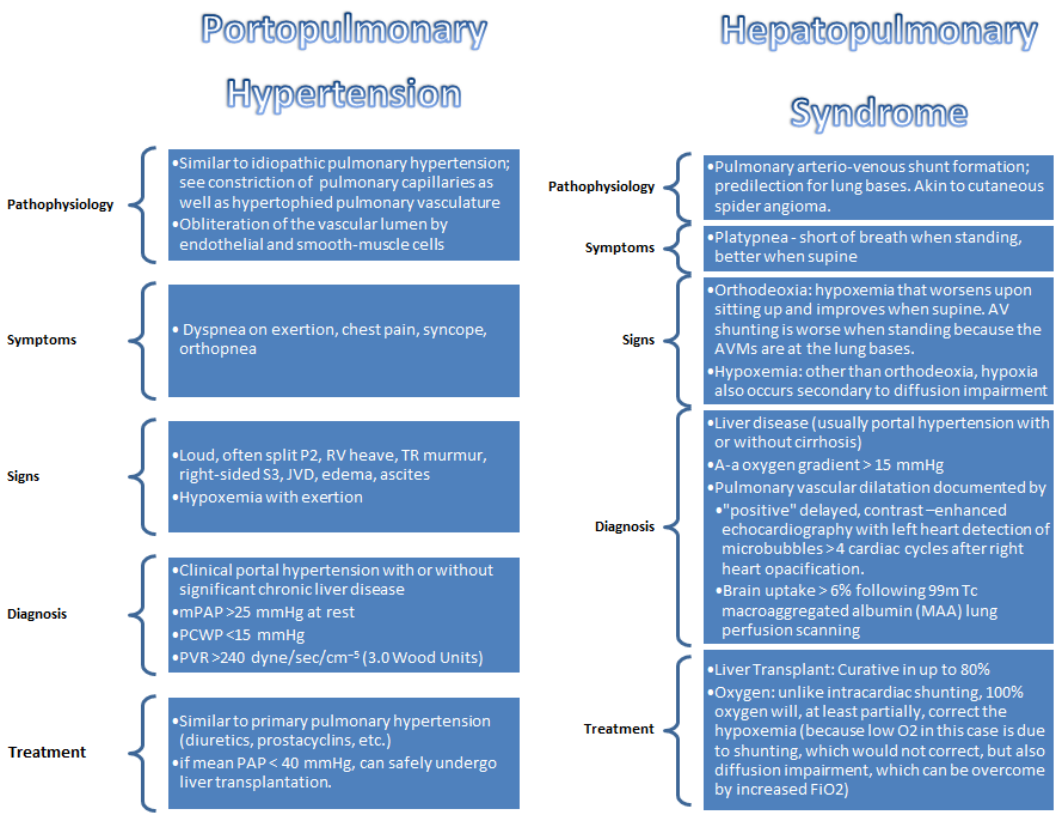


Figure 10. Port-Pulmoary & Hepato-Pulmonary

PAH associated with Congenital heart disease:

Seen as a complication due to un corrected congenital heart disease with increased pulmonary blood flow and systemic and pulmonary shunting. The condition is defined as Eisenmenger syndrome characterised by progressive pulmonary vasculopathy with shunt reversal resulting in cyanosis. Prognosis is better when compared to other causes

of PAH as the right ventricle adaptive response seen in congenital heart disease[25]

Eisenemenger Physiology	Reversible PAH	Irreversible PAH
Symptoms	**Most Class 1** and few class 2	**All class 4** And most class 3
Functional capacity	6 minutes > 400mts walk	6 minutes walk < 250 m
Systemic O2 saturation	**> 90-95 %**	**< 90 %** At room Air
Signs of increased pulmonary flow	Well Split S2 Dynamic RV LV still felt Mitral MDM	Quiet pre-cardium No-Mitral MDM Absent LV impulse
Signs of gross RV failure	**Definitely Irreverisble** (Simple TR, V waves not enough to diagnose RV failure .Mean JVP should be elevated)	
Pulmonary artery Systolic pressure (PASP)	**Use-less for two reasons** 1.In any large VSD RV systolic pressure is at near equilibrium of LV . 2. RV function has a major impact on PASP	
Pulmonary Diastolic pressure (PADP)	< 40mmhg	> 40mmhg
Pulmonary artery pulse pressure (PAPP)	**< 30 mmhg**	**> 50mmhg**
Note : Operability depend upon many factors other than reversibility of PAH. ***Reversibility and operability are not synonymous*** .There have been many instances of low PVR doing badly after VSD closure. So The intrinsic RV function can be crucial determinant of surgical outcome		

Figure 11. Eisenmenger Physiology

Diagnosis:

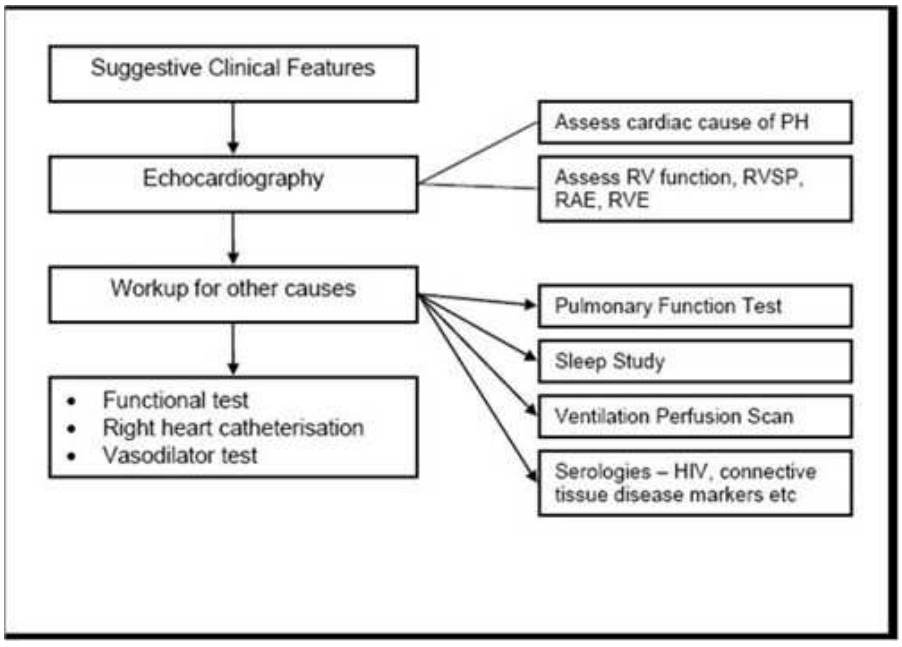
Symptoms:

Exertional dyspnoea is the most common presenting sysmptom seeni 60% cases. Followed by increased fatigability in 19% cases. Syncope seen more frequently in IPAH. As the disease advances patient develop syncope, increasing dyspnoea, later right ventricular failure

causing abdominal distension , pedal odema[26]. The symptoms from the risk factors causing PH like CTD, COPD, cardiac illness could mask or aggravate the symptoms of PH. This has resulted in delay in diagnosis with average of 2 years since onset of symptoms.

Physical signs:

SIGN	IMPLICATION
Physical Signs That Reflect Severity of Pulmonary Hypertension	
Accentuated pulmonary component of S_2 (audible at the apex in >90%)	High pulmonary pressure increases the force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of the pulmonary valve into a high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S_4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular a wave	Poor right ventricular compliance
Physical Signs That Suggest Moderate to Severe Pulmonary Hypertension	
Moderate to severe PH	
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Increased jugular v waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced PH with right ventricular failure	
Right ventricular S_3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction, tricuspid regurgitation, or both
Hepatomegaly	Right ventricular dysfunction, tricuspid regurgitation, or both
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction



Electrocardiogram:

Inexpensive and non invasive tool, but not sensitive or specific to PH. Common findings are right axis deviation, right atrial and ventricular enlargement, sometimes right ventricular hypertrophy with strain pattern[27]

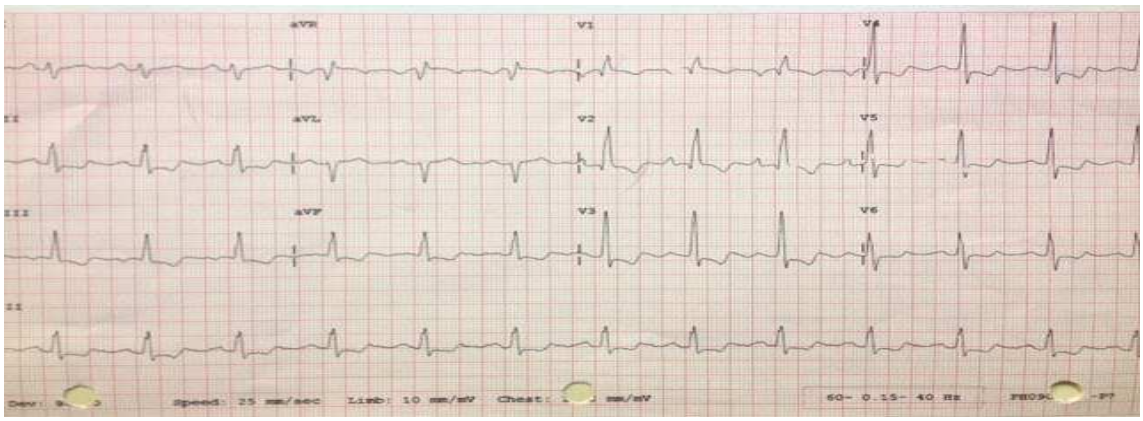


Figure 12. ECG in Pulmonary Hypertension

CHEST X RAY:

On the lateral view, right ventricular enlargement can be seen. Presence of engorged pulmonary artery shadows at the centre with pruning of peripheries helps in diagnosis of pulmonary hypertension. Pulmonary venous congestion is in left sided heart disease. Emphysematous chest showing hyperinflation with flattening of diaphragm in cases of COPD[28].

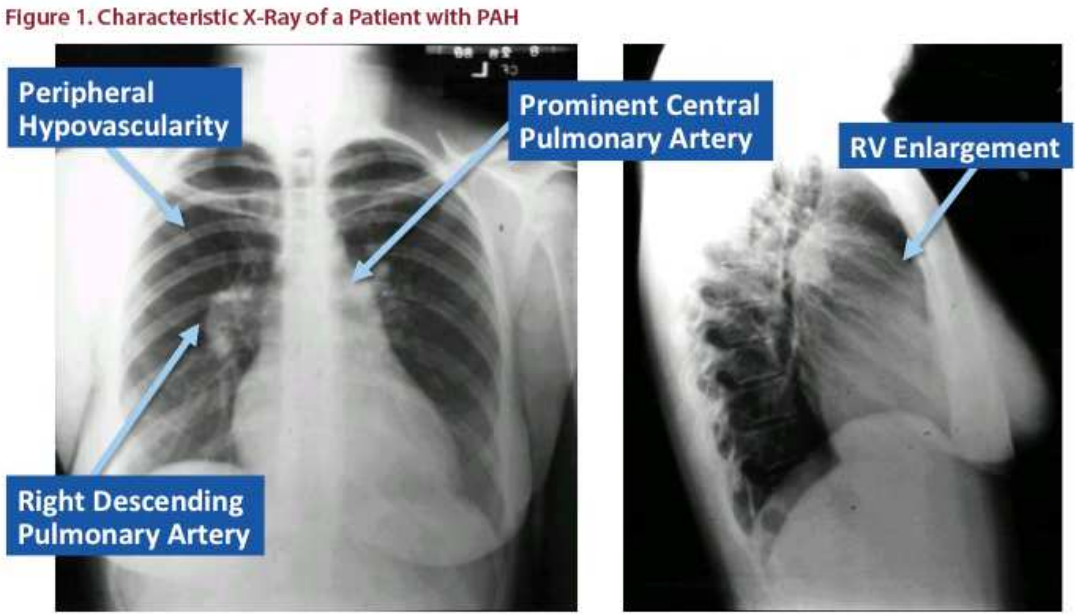


Figure 13. X - Ray

ECHOCARDIOGRAM:

It is a non-invasive screening tool used in suspected pulmonary artery hypertension patients. Pulmonary artery pressure determined by using Doppler echocardiography more than 35 mmhg is cut off for diagnosis of pulmonary hypertension[29]

Echocardiogram measures the following parameters:

1. Pulmonary artery systolic pressure (PASP)
2. Assessment of left ventricular –systolic, diastolic function and valves
3. Assessment of RV dysfunction
4. Presence of poor prognostic factors.

1.Pulmonary artery systolic pressure (PASP):

This depends on the principle that in the absence of right ventricular outflow tract obstruction PASP equals the right ventricular systolic pressure (RVSP)

PASP = RVSP= 4 $(V_{TR})^2$ + RAP according to the Bernoulli equation

When V_{TR} is less than 2.8 m/s and PASP less than 36 mmhg PH is less likely.

2. Assessment of left ventricular function:

This helps to find out the cardiac cause for pulmonary hypertension.

- Left ventricular systolic function:

a) Fractional Shortening(FS)

It is calculated using M mode in echo, measuring the distance between the two endocardial borders above the papillary muscles.

FS = ((LVEDD-LVESD) / LVEDD) x 100

Where LVEDD is the left ventricular diameter end of diastole

LVESD is the left ventricular diameter end of systole.

b) Ejection Fraction:

Normal more than 55

Mild – 45 to 54

Moderate- 30 to 44

Severe less than 30

- Left ventricular diastolic function:

  Mitral E and A wave ratio:

  E wave – diastolic filling of left ventricle before R wave in ECG

  A wave- atrial filling after P wave in ECG

  Normal E/A ratio is 1.32+ 0.42

- Valves:

  Mital valve abnormalities are the most common association found with pulmonary hypertension.

3. Assessment of right ventricular dysfunction:

- RV hypertrophy- free wall thickness more than 5 mm
- RV dilatation- mild when RV forms 60 to 100 % of LV area

  Moderate when RV equals LV

  Severe when RV more than LV or cardiac apex is by RV

- TAPSE- tricuspid annular plane systolic excursion
- Tricuspid regurgitation –severity
- Hepatic vein Doppler- reversal of flow shows severe PH

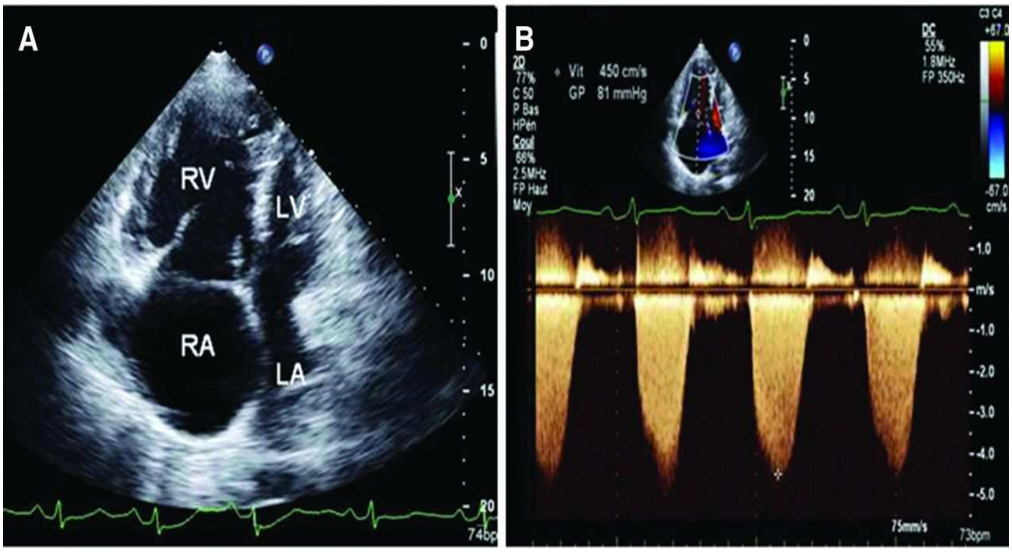
5. Poor prognostic factors:

    - Marked right atrial dilataion
    - Pericardial effusion
    - Right ventricular dysfunction
    - D shaped LV
    - Tei index- myocardial perferomance index

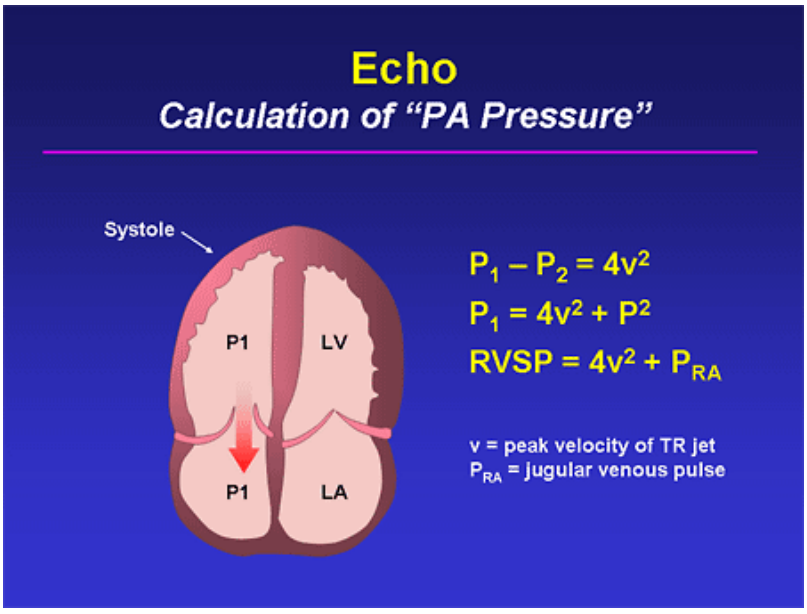
Figure 14. Echocardiogram, A,B,C

Dilated Right ventricle compressing the left ventricle causing ‘D’ shaped left ventricle[30,31].

Massive dilatation of right atrium and ventricle with tricuspid valve regurgitation



Tricuspid regurgitation jet velocity is found then mPAP is calculated using the modifed bernouli equation. This corresponds to RA to RV pressure gradient of more than 31 mmHG and the estimated RA pressure of 5 mmhg[32].



Grading of pulmonary arterial hypertension*			
	Systolic	Diastolic	Mean
Grade 1 (Mild)	30-50	20-25	>30
Grade 2 (Moderate)	50-70	26-35	>40
Grade 3 (severe)	70-110	36-45	>50
Grade 4 (Systemic or supra systemic)	>110	46-55	>60

*Data from 100 patients of PAH and rheumatic heart disease. Quintile 1 & 2 (Grade 1) qunitile 3 & 4 (Grade 2) quintile 5 (Grade 3) top 3%(Grade 4)

VENTILATION – PERFUSION SCAN:

It is ideal and more specific in diagnosing pulmonary hypertension due to CTEPH. In VP scan there will be a segmental or large perfusion defects. If CTEPH is still inconclusive, an invasive pulmonary angiogram with contrast to be done which shows pouches, webs , bands and even complete vascular occlusion[33].

PULMONARY FUNCTION TEST:

In group 1 PAH, there will be a moderate lung restriction pattern so it can be evident in pulmonary function test. In patients with scleroderma, there will be a reduced diffusion capacity of carbon monoxide which is a warning sign for developing Pulmonary Artery Hypertension.

CARDIAC MAGNETIC RESONANCE IMAGING (CMR):

It is not useful in diagnosing PAH, but helps in assessing the right ventricular function and also in assessing the CHD. Right ventricular ejection fraction less than 35% on CMR is predictive of mortality

OXIMETRY:

A overnight oximetry is done in identifying the patient with obstructive sleep apnea. Formal polysomnography is done in patients with desaturation at night.

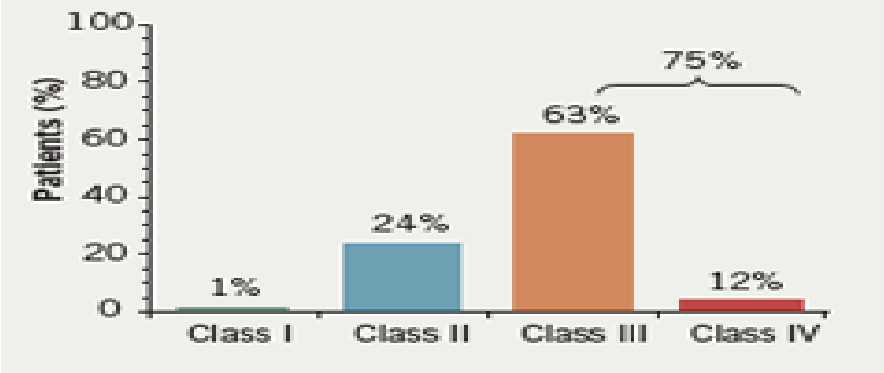
FUNCTIONAL ASSESSMENT:

Functional assessment following disease progression or the treatment response are based on the 6 Minute Hall Walk (6MW). It is one of the prognostic indicator for assessing the patients with PAH. It is still on research but it is still the primary endpoint in clinical trials in assessing the PAH[3435].

WHO gave the functional classification of patients for pulmonary hypertension similar to NYHA. Is useful in initial assessment , further prognosis and the response to treatment.

Table 2 – World Health Organization functional classification for pulmonary hypertension

Functional class	Symptoms
Class I	*Symptoms do not limit physical activity.* Ordinary physical activity does not cause undue discomfort.
Class II	Slight limitation of physical activity. The patient is comfortable at rest, yet experiences *symptoms with ordinary physical activity*.
Class III	Marked limitation of activity. Patient is comfortable at rest, yet experiences *symptoms with minimal physical activity.*
Class IV	Inability to carry out any physical activity. The patient may experience *symptoms even at rest.* Discomfort is increased by any physical activity. Manifest signs of right-sided heart failure.



Adapted from AJRCCM 2006;173:1023–1030

Key: NYHA—New York Heart Association

The other important way of assessing the exercise capacity and gas exchange is by doing cardiopulmonary exercises. Peak systolic blood pressure less than 120mmHg and peak oxygen uptake less than 10.4 mL/Kg/min is a poor prognostic indicator

DETERMINANTS OF RISK	LOWER RISK (GOOD PROGNOSIS)	HIGHER RISK (POOR PROGNOSIS)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (>400 meters)	Shorter (<300 meters)
CPET	Peak Vo_2 >10.4 mL/kg/min	Peak Vo_2 <10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP <10 mm Hg, CI >2.5 L/min/m^2	RAP >20 mm Hg, CI <2.0 liters/min/m^2
BNP§	Minimally elevated	Significantly elevated

*Most data available pertain to IPAH, with little data available for other forms of PAH. One should not rely on any single factor to make risk predictions.
†The WHO class is the functional classification for PAH and is a modification of the NHYA functional class.

RIGHT HEART CATHETERISATION:

It is the invasive procedure done at the end, if all other non-invasive procedure proved to be inconclusive but still PAH could not be ruled out.

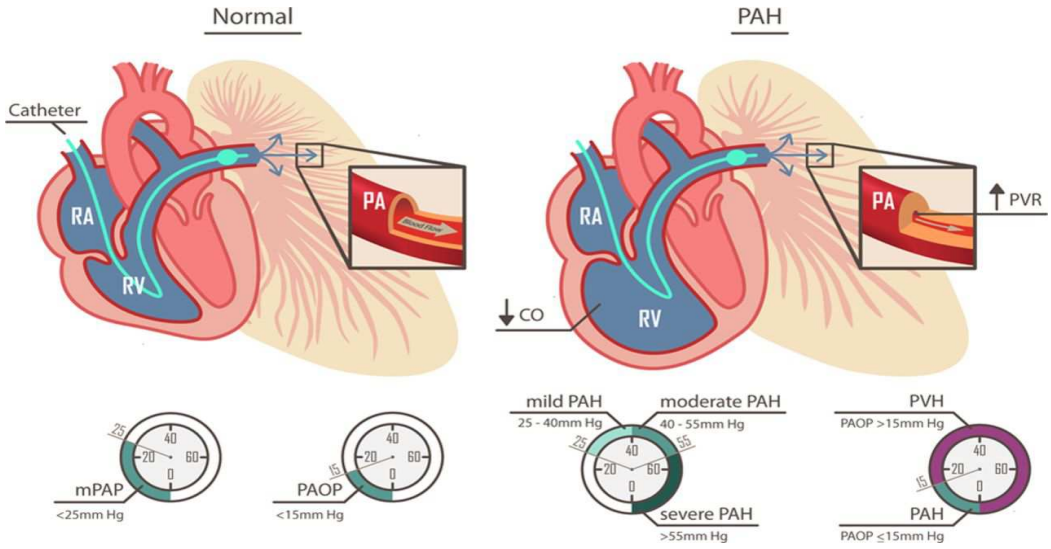
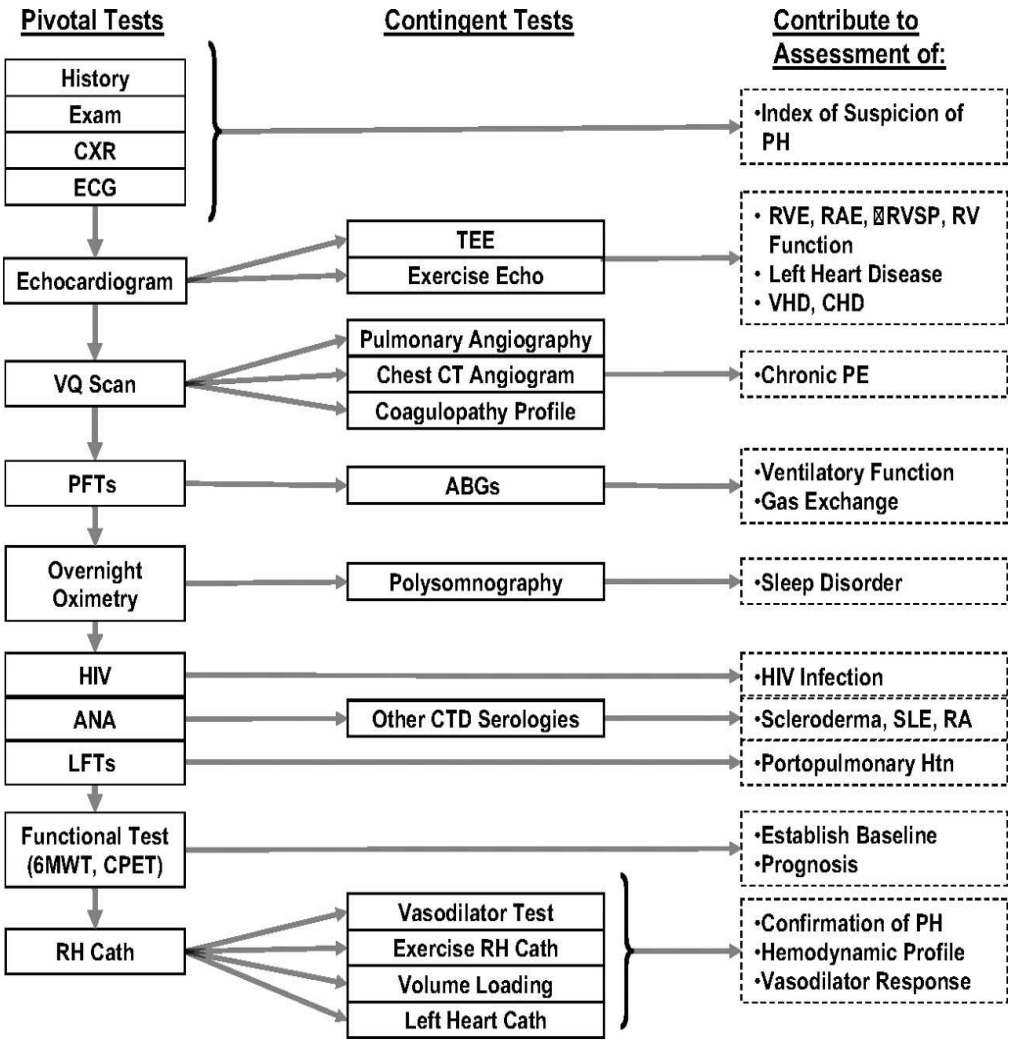


Figure 15. Right Heart Catheterisation

The measurements that are done during the RAH are:

1. Oxygen saturation in SVC, IVC, pulmonary and systemic arteries
2. Right Atrial and Right Ventricular pressure
3. Pulmonary artery pressure
4. Left side filling pressure
5. CO/ cardiac index
6. PVR
7. Systemic blood pressure
8. Heart rate
9. Response to acute vasodilators

The commonest mistake in diagnosing the PAH is misinterpreting the PAWP values. It should be measured at different segments of the pulmonary vasculature and at the end expiration. Acute vasodilator testing should be performed in the patients with IPAH[36].



TREATMENT:

Goals of the treatment in PAH are to improve the symptoms, right ventricular function, hemodynamics, exercise tolerance and thereby improving the survival.

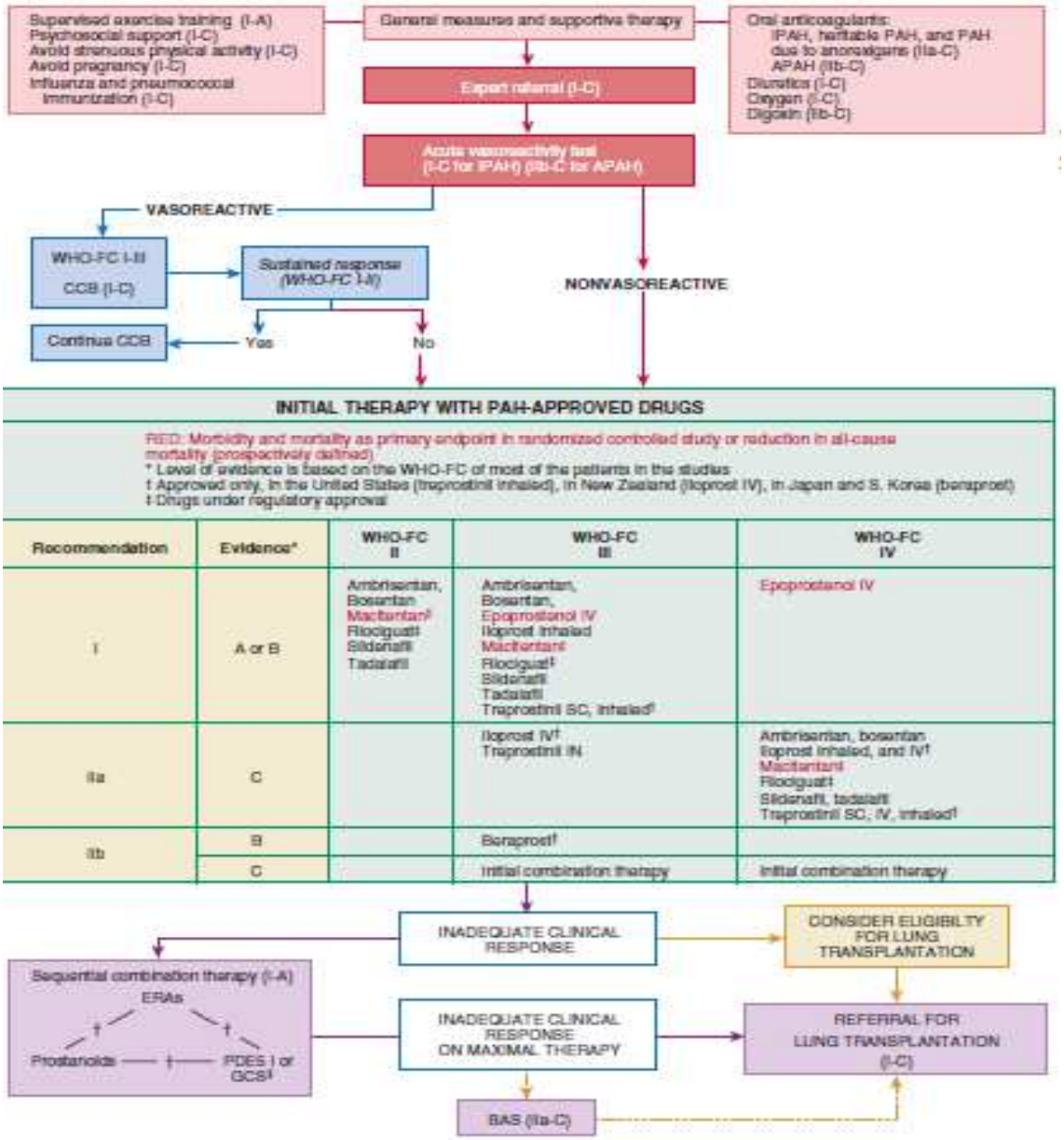


Figure 16. Treatment Algorithm

GENERAL MEASURES:

- Graded low level aerobic exercises are allowed to do but heavy physical exertion and isometric exercises should be avoided.
- Intensive pulmonary rehabilitation proved to be useful in some patients.
- Oxygen therapy in order to maintain the saturation at 92% or above.(it may not be possible in patients with intracardiac shunting)
- Sodium restricted diet (< 2400 mg/day) is advisable especially in patients with right heart failure.
- Immunisation against influenza and pneumococcal are mandatory.
- Hemodynamic fluctuations during pregnancy is very difficult to manage and maternal mortality reaches almost 50%. Hence better to terminate pregnancy in patients with PAH.

ANTICOAGULANTS AND DIURETICS

Anticoagulants are useful in treating patients with PAH, particularly with Idiopathic PAH. Warfarin is the prescribed drug and the dosages are adjusted in such a way that INR is maintained between 1.5 and 2.5.[37]

Diuretics are used in patients with right heat failure with volume overload. Care has to be taken that there should not be any electrolyte imbalance or deteriorating renal function.

CALCIUM CHANNEL – BLOCKERS

It is helpful in those patients with PAH who are good responders to the acute vasodilator testing. Positve response to this test is defined as fall in mPAP of atleast 10mmHg to a mPAP of 40mmHg or less with unchanged or increased CO. those patients who met this criteria but does not improve with this drug should not be considered as chronic responders and should find an alternate PAH therapy. IPAH in some patients (< 7%) responds to calcium channel blockers. Drugs used are nifedipine, diltiazem and amlodipine[38]. Verapamil should be avoided because of its negative inotropic effects.

PROSTANOIDS

The absent or reduced prostacyclin synthase in PAH is one of the important pathophysiology mechanism. Prostacyclin I_2, which is a vasodilator with antiproliferative effects are not synthesised in PAH[39]. Many treatment protocols are aimed at it. Commonly used prostanoids are :

- Epoprostenol – continuous intravenous, dosage to start with 2 ng/kg/min and can be titrated upward with maximum dosage of 25 – 40 ng/kg/min[40,41,42].
- Treprostinil – continuous subcutaneous, intravenous and intermittent inhaled. The dosage is maximum of 75 – 150ng/kg/min[43,44,45].
- Iloprost – intermittent inhaled[46].

Inhaled prostacyclin analogues shows superior results in improving pulmonary hemodynamics and functional capacity and also in reducing the worsening of pulmonary hypertension.

ENDOTHELIN RECEPTOR ANTAGONIST:

The Endothelin-1 is a potent vasoconstrictor which contributes to the pathogenesis of PAH. The commonly used endothelin receptor antagonist used in the treatment of PAH are:

1. Bosentan – It is helpful and highly effective in patients with congenital systemic-to-pulmonary shunts and Eisenmenger physiology[47,48,49]. After drug therapy, there is improvements in PVR, mPAP and 6MW distance and also there is no worsening of oxygen saturation. Liver function to be monitored.

2. Ambrisentan – Same as bosentan. Liver dysfunction is not so significant.
3. Macitentan – It is used as a dosage of 3mg or 10 mg daily[50].

PHOSPHODIESTERASE INHIBITORS:

The derangements of cyclic Guanosine Monophosphate (cGMP) pathway due to reduced NO synthesase is the another pathogenesis in PAH. PDE5 inhibitor drugs like Sildenafil 20mg thrice daily helps in inhibiting the hydrolysis of cGMP and thereby improving the symptoms of PAH[51]. Tadalafil is another drug which is used as 40mg single dose[52].

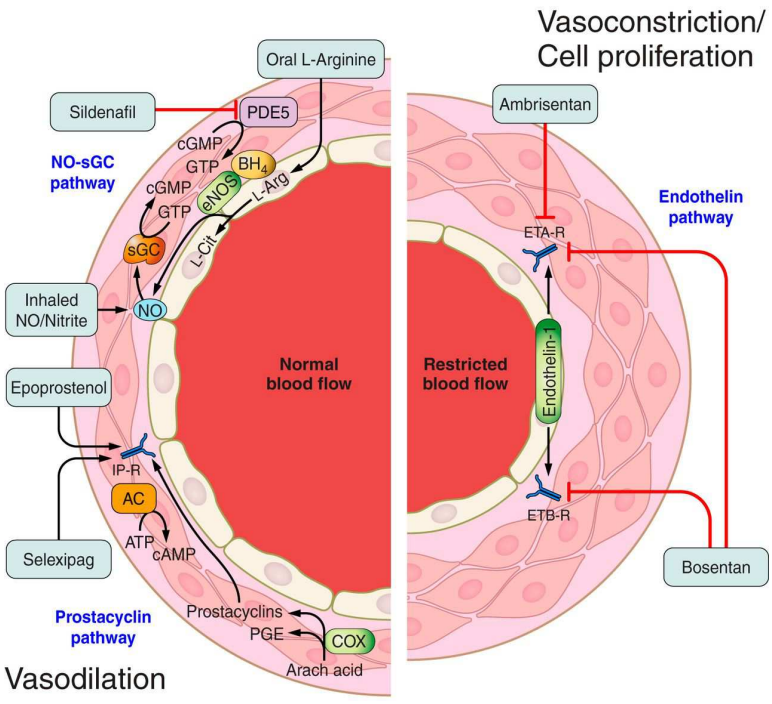


Figure 17. Sites of drug action in Pulmonary Vasculature

SOLUBLE GUANYLATE CYCLASE STIMULATORS:

Riociguat[53,54,55], it directly stimulates the soluble guanylate cyclase and increases the sensitivity of it to NO. it should not be used along with PDE5 inhibitors.

DRUGS ON RESEARCH:

Selexipag – Selective prostacyclin receptor agonist.

Imatinib – Used in refractory PAH and it improves PVR and CO.

Nilotinib, serotonin transport inhibitor escitalopram, oral prostacyclin analogues Beraprost, inhaled NO and sodium nitrate preparations are ongoing trials

INTERVENTIONAL THERAPIES:

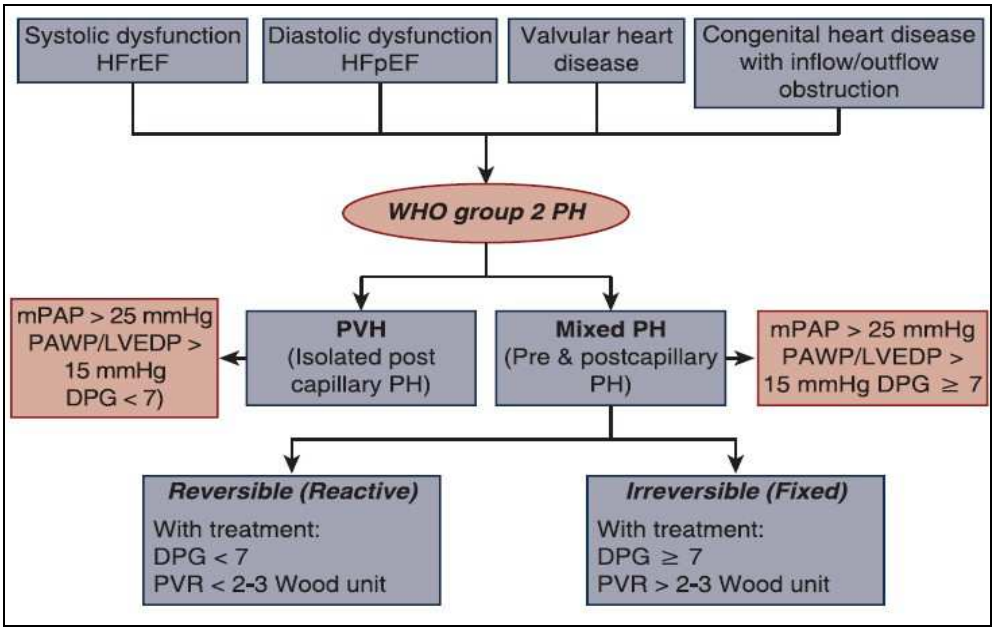
1. Atrial septostomy – It creates an increased right to left interatrial shunt and decreases the right heart filling pressure and thereby improving the symptoms of PAH.
2. Graded balloon dilatation of the fossa ovalis is the another procedure
3. Transplantation – lung or heart lung transplantation is used as a final resort.

GROUP 2. PH BY LEFT SIDED HEART DISEASE:

Presence of chronic left sided ventricular systolic or diastolic dysfunction or valvular lesions results in persistent elevation of left atrial pressure there by causing passive backward transmission of pressure to pulmonary veins . Characterised by elevation pulmonary artery wedge pressure more than 15 mmhg, with normal transpulmonary gradient and pulmonary venous resistance.

Common causes are mitral and aortic valve disease, pericardial disease, cardiomyopathies, left ventricular dysfunction age related changes. Out of all heart failure, preserved ejection fraction (HFpEF) is now found to be more common cause.

Figure 18. Management of Group 2 PHT



Right ventricle is not affected in the early stage of the disease. It adapt itself to the elevated afterload with hypertrophy. If the disease progress further, it may go for right ventricular dysfunction. Hence right ventricle is the lastly affected in pulmonary venous hypertension.

DIAGNOSIS:

HFpEF is the commonest cause and is often mistaken with IPAH in the diagnosis[56]. It occurs in patients with older than group 1. Orthopnea, paroxysmal nocturnal dyspnea are pathognomonic

Figure 19. Difference between PAH & HFpEF

CHARACTERISTIC	PAH MORE LIKELY	HFPEF MORE LIKELY
Age	Younger	Older
Comorbid conditions—DM, HTN, CAD, obesity (metabolic syndrome)	Often absent	Often multiple present
Symptoms—PND, orthopnea	Often absent	Often present
Cardiac examination	RV heave, loud P_2, TR murmur	Sustained LV impulse, LS4
CXR	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	RAD, RVE	LAE, LVE, atrial fibrillation, no RAD
Natriuretic peptides	Often elevated	Often elevated
Echo—LAE, LVH	Absent	Often present
Echo—diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echo—right ventricle	Often enlarged, may share the apex	Often normal, mildly enlarged
Echo—pericardial effusion	Sometimes	Rare

Chest X Ray – pulmonary vascular congestion, interstitial edema on radiograph

CT Chest – Mosaic perfusion pattern and ground glass opacities

ECG – Left ventricular and atrial enlargement, atrial fibrillation.

Echocardiogram – Left ventricular hypertrophy, left atrial enlargement and Doppler showing diastolic dysfunction.

Two types of hemodynamic profiles are seen:

1. Elevation in Pulmonary Arterial Pressure with only a slight increase in transpulmonary gradient (mPAP - PAWP).

   In preserved right ventricle, a high systolic pressure is generatd to maintain adequate forward blood flow. So moderate degree of PH is characteristic and favourable.
2. Some patients will have elevated pulmonary arterial pressure due to reactive pulmonary vasoconstriction. They will have characteristic elevation in pulmonary artery diastolic pressure.

TREATMENT:

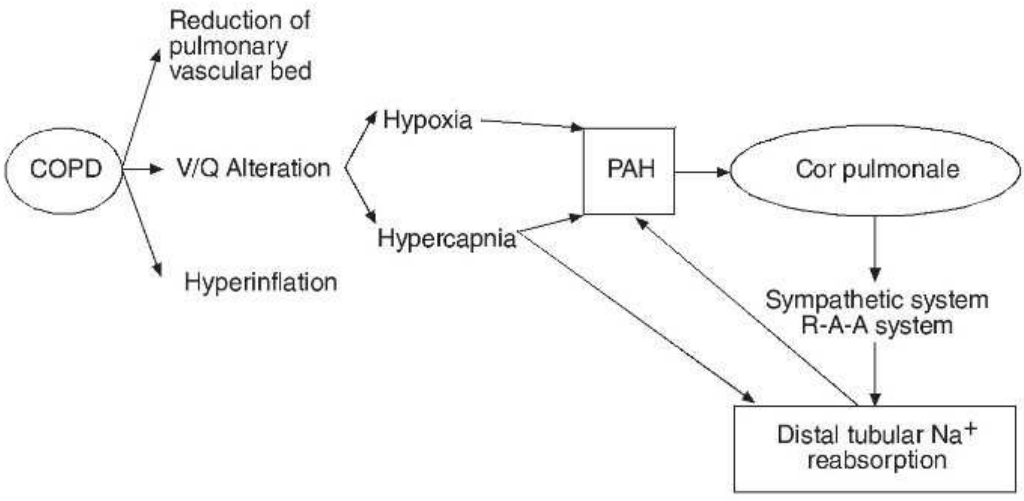
1. Treat the underlying cause.
2. Blood pressure to be controlled.
3. Volume management.

4. Sodium restriction diet.
5. Comorbid diseases like obesity. Diabetes to be addressed.
6. Maintain sinus rhythm as these patients will not tolerate atrial fibrillation.
7. No role in PAH specific therapy.

GROUP 3: PULMONARY HYPERTENSION CAUSED BY CHRONIC RESPIRATORY DISEASES:

In the chronic lung diseases, there will be alveolar hypoxia, leading to pulmonary vasoconstriction and remodelling resulting in pulmonary hypertension. Generally, in respiratory pathology, mPAP is less than 40mmHg i.e., mild to moderate pulmonary hypertension. Severe pulmonary hypertension is rare[57,58]. Progression of natural history of pulmonary hypertension is low in patients with COPD (0.5mmHg/year).

Figure 20. COPD & PH



Echocardiographic screening in patients with COPD is difficult and hence the severity could not be assessed. mPAP is inversely correlated with PaO_2. With the knowledge of FEV_1, PaO_2, and mPAP, patients could be classified into 4 groups namely,

1. Normal mPAP, moderately decreased FEV_1 and PaO_2.
2. Moderate mPAPand PaO_2, severely decreased FEV_1.
3. High mPAP, Severely decreased PaO_2, FEV_1.
4. Severe mPAP and severly decreased PaO_2 and moderate reduction in FEV_1.

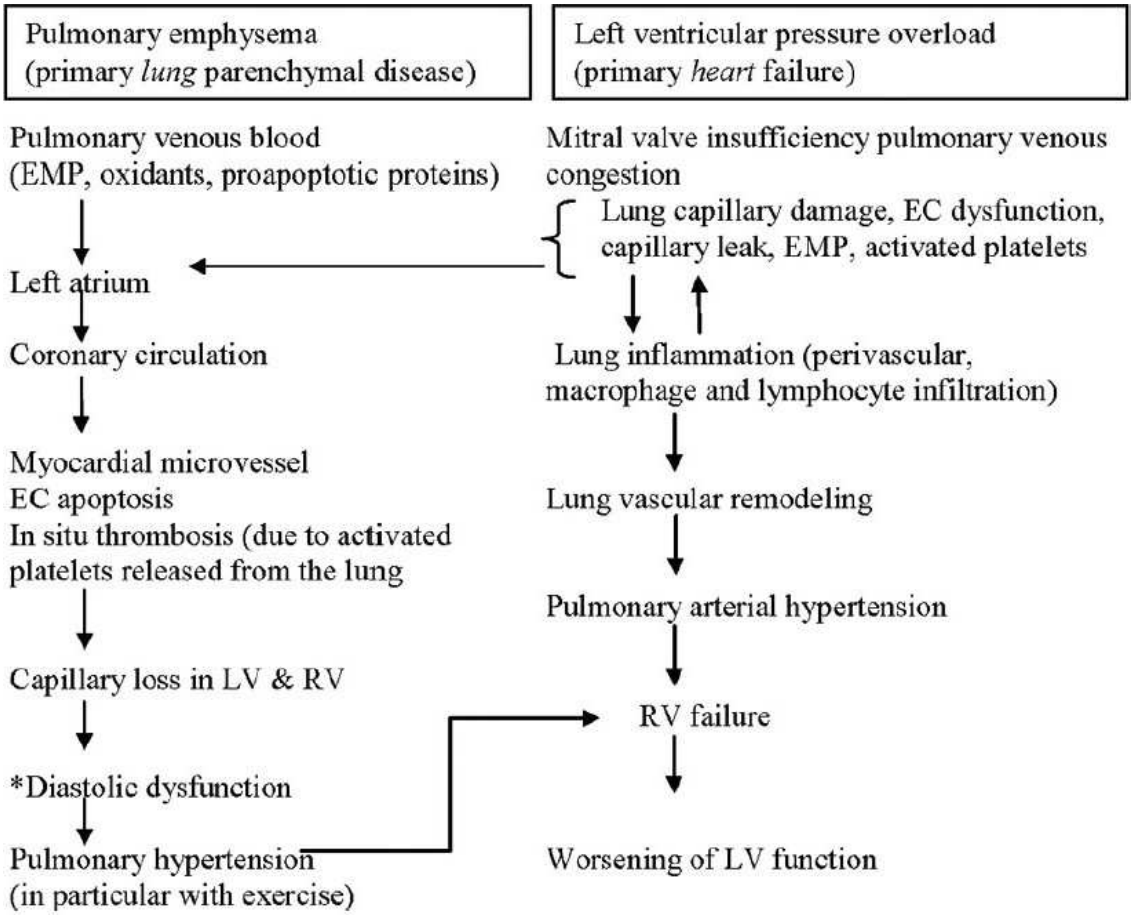
The last group has high FEV_1 and mPAP but lower PaO_2 than the other groups suggesting alteration in pulmonary vasculature. These patients may have other comorbid conditions favouring diastolic and systolic dysfunction, obstructive sleep apnoea etc. These patients have severe exertional dyspnea, poor prognosis than other COPD patients[59,60].

DIAGNOSIS:

As patients have nonspecific signs and symptoms pertaining to cardiac and respiratory pathology, it is difficult to differentiate both. Spirometry, arterial blood gas analysis, diffusion capacity for carbon monoxide are important for diagnosis. BNP is also elevated but it can occur in both left heart and right heart failure.Doppler echocardiography

is suboptimal in diagnosing COPD induced PH. However the gold standard in diagnosing PH is RHC, which determines the precapillary PH and the hemodynamic severity excluding the post capillary component. Always it is important to keep in mind the comorbid conditions like left heart failure, obstructive sleep apnoea etc as they also contribute to the clinical findings.

Figure 21. PH due to Cardiac & Lung Disorder



TREATMENT:

Smoking cessation is very important and it is first and foremost to prevent further progression of the disease. Long term Oxygen therapy is helpful and it results in decreased mPAP.pharmacological drugs like calcium channel blockers, PDE5 inhibitors are tried but they have deleterious effect in the alveolar gas exchange. The ideal management in the end stage disease is lung transplantation. Even PH due to other lung disease like sarcoidosis, Interstitial lung disease, Pulmonary Langerhans cell histiocytosis and lymphangioleiomyomatosis all lead to end stage lung disease will warrant a lung transplantation.

GROUP 4. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH):

It is a curable form of pulmonary hypertension which often requires surgical management. It is diagnosed by certain findings which persists after 3 months of continuous anticoagulant therapy. These findings are, at least one segmental perfusion defect seen in CT angiography or lung scanning and presence of precapillary type of pulmonary hypertension. CTEPH is due to pulmonary embolism obstructing the main pulmonary arteries. Incidence being 3 to 30 million population is often misdiagnosed. Error mainly due to referral bias, difficulty in diagnosis of pulmonary hypertension in acute pulmonary

embolism due to lack of specific symptoms in the acute stage. Acute venous thromboembolism is an independent risk factor. Prothrombotic factors lupus anticoagulant, antiphospholipid antibodies, factor 8 are associated with it. Due to hyper coagulation, increase platelet count and inability to cleave fibrinogen, contribute to the obliteration of pulmonary arteries. Median age at diagnosis is 63 years, occurring equally in both sexes.

DIAGNOSIS:

Non-specific signs and symptoms pertaining to right sided heart failure like oedema, abdomen distension is found. In contrast to IPAH, these patients have haemoptysis, disease is suspected with the presence of risk factors. Imaging modalities like CT, ventilation perfusion scan aid in the diagnosis. Presence of atleast one defect involving more than half of a segment of lung is diagnostic in ventilation perfusion scan. But some patients may have nonsegmental and smaller defects especially in PAH and PVOD.

RHC will show prcapillary PH. The prognostic indicator after surgery is the PVR. Contrast enhanced CT shows, stenosis, complete obstruction, arterial wall irregularities, pulmonary artery webs and bands. Side selective pulmonary angiography in both anteroposterior and lateral

views helps in assessing the involvement of the proximal segment and evaluating the surgical accessibility.

TREATMENT:

Surgery is the treatment of choice in CTEPH. Embolectomy and pulmonary endarterectomy are the surgical procedures done in CTEPH. Based on the specimen it can be divided into four types:

Type I : Involving main and lobar pulmonary arteries with red thrombus and white obstruction.

Type II: Intimal thickening and fibrosis in proximal to segmental arteries.

Type III: Thickening, fibrosis and intimal webbing involving distal segmental and subsegmental arteries

Type IV: Microscopic distal arteriolar vasculopathy without visible thrombus. Type IV is not operable.

Operable Criteria:

- NYHA functional class II, III or IV
- Preoperative PVR more than 300 dyne-sec.cm^{-5}
- Surgical accessibility of thrombi in main, lobar or segmental arteries
- Reasonable relationships to hemadynamic severity

- Absence of severe comorbid disease

After surgery most of the patients are relieved of symptoms and anear normal haemodynamic stability occurs. Medical treatment also attempted in CTEPH[61] and they are lifelong anticoagulants with vitamin K antagonists, diuretics, oxygen supplementation. Soluble guanylate cyclase stimulator, riociguat helps in improvement of 6MW and PVR.

GROUP 5. PH WITH UNCLEAR OR MULTIFACTORIAL CAUSE:

Multiple mechanisms contribute to the pathogenesis of pulmonary hypertension like hyperdynamic circulation causing congestive cardiac failure, intrapulmonary haematopoiesis can cause obstruction to pulmonary arteries, porto pulmonary hypertension are seen following certain hematologic disorders especially with myeloproliferative diseases. splenectomised individuals either post traumatic or following hematologic disorders favours development of distal CTEPH or IPAH

Some of haemolytic anaemia like sickle cell disease[62], beta thalassemia are associated with PH. They can cause post capillary PH due to hyperdynamic circulation or precapillary PH by producing pulmonary vascular remodelling. Most commonly associated with sickle cell disease the incidence being 6%.

Systemic disorders:

Sarcoidosis:

It is a chronic granulomatous disease of unknown etiology. It causes fibrosis of the pulmonary capillary bed resulting in hypoxia. As the severity is out of proportion to the degree of destruction other causes were considered like cardiac sarcoidosis, mediasternal lymphadenopathy causing compression of pulmonary vessels, etc. Treatment tried with steroids[63].

Pulmonary Langerhans cell histiocytosis:

Even though a rare disease it is seen in younger individuals with smoking history. Causes parenchymal destruction and vasculopathy changes. Poor prognosis. Treatment being lung transplantation[64]

Other systemic disoreders like lymphangioleiomyomatosis and Neurofibromatosis are also associated with PH with multiple unclear mechanisms of causation.

Metabolic disorders:

Enzyme deficiency disorders like type 1 a glycogen storage disease due to glucose 6 phosphate deficiency, Gauchers disease due to

lysosomal B glucosidase deficiency can cause thromboembolic or restrictive lung disease attributing to pulmonary hypertension

Miscellaneous:

Rare conditions like pulmonary artery sarcomas, metastatic tumor emboli from breast,lung or gatric cancers, fibrosing alveolitis, end stage liver disease on lomg term haemodialysis are also associated with pulmonary hypertension.

Platelets:

They are anucleate small (3.0 x0.5µm) discoid shaped cells, fragmented from megakaryocytes stimulated by thrombopoietin produced by liver[65]. These stimulated megakaryocytes undergo endomitosis and there by sends cytoplasmic projections called proplatelets. Each megakaryocyte gives rise to 1000 to 2000 platelets. Normal paltelets cytoplsmic volume is 7fl. Younger platelets are larger than those present in circulation due to abundant cytoplasm. They are some times counted along with RBCs due to their larger size. Half life of platelets is 8 to 10 days.

Platelets in various stages of activation from rest, partial to full actiavtion from left to right.

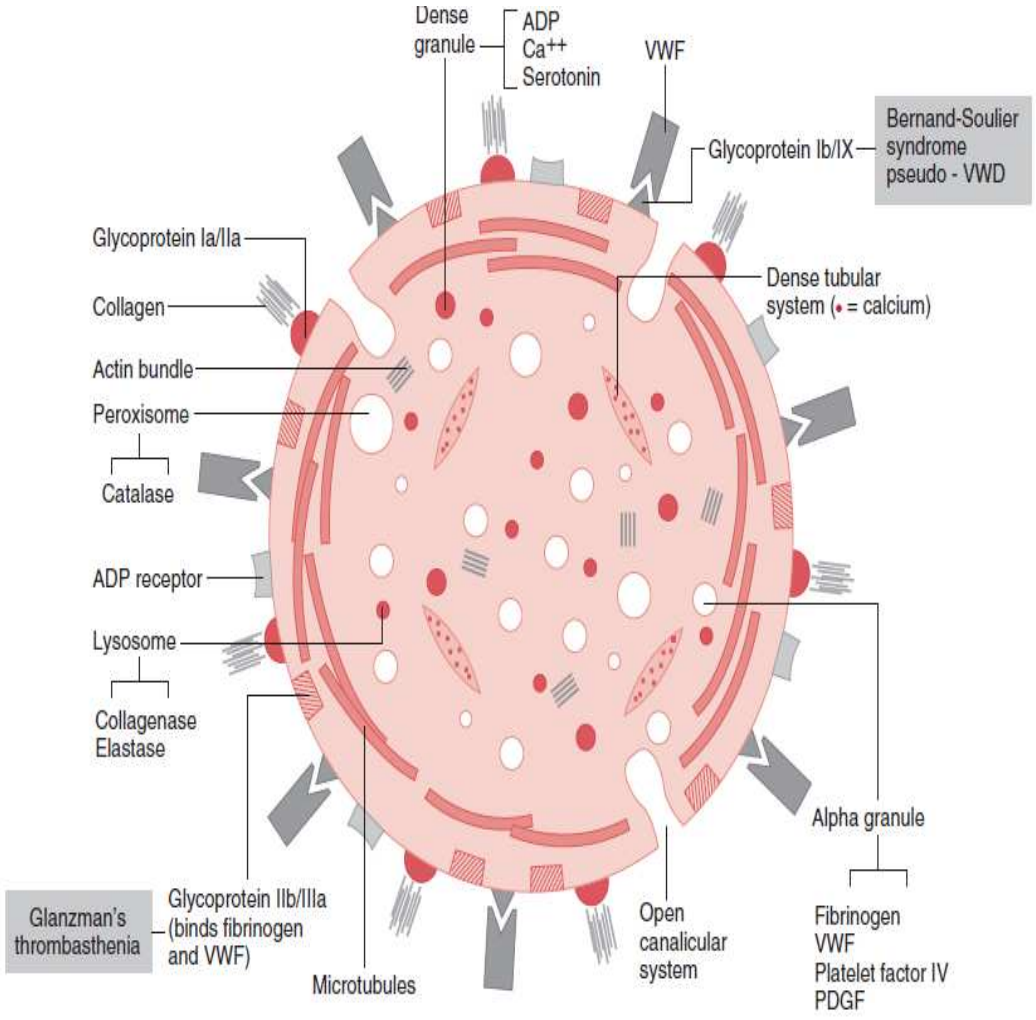
In peripheral smear stained by wright’s stain, they appear as blue grey cells with purple red granules measuring one tenth of size of red blood cells. Normal thrombocyte count is 1,50,000 to 4,00,000 per µl. One third of the platelet pool is sequested inside the spleen and released into circulation in times of demand. It is referred as the marginal pool. Epinephrine causes release in times of stress. Aged platelets are destroyed in spleen.Platelets contain numerous granules which are released on activation.

Alpha granules :

Contain vwf, fibrinogen, procoagulant factor v, growth factors PDGF and TGF- beta, platelet factor 4(PF4) also called as heparan. PF4 functions as a heparan inactivator by binding with the endogenous heparan sulphate at the site of injury and helps in clot formation. Growth factors play important role in smooth muscle, fibroblast proliferation and repair.

Dense granules:

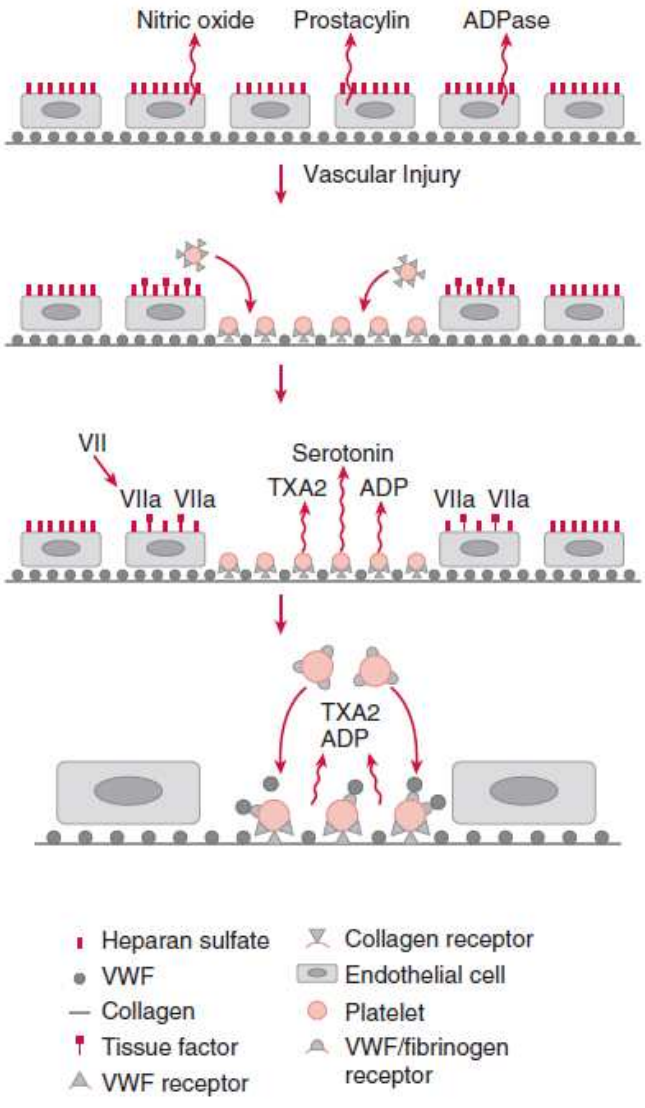
Each platelet contains 3 to 8 dense granules. They are secreted rapidly into the circulation when activated. They contain ADP, calcium and serotonin. ADP is important in activation of platelets and causes recruitment of other platelets. Serotonin increases vascular tone by causing vasoconstriction. Calcium causes actin- myosin chain contraction in the cytoskeleton of platelets causing shape change. It also helps in coagulation cascade and collagen crosss linking. In addition calcium forms a co factor for phospholipase c , enzyme involved in formation of arachidonic acid and further reactions leading to formation of thromboxane A2[66].



Platelets are seen as individual cell circulating inside blood vessels not interacting with other platelets or cells. But equipped with extensive capacity to adhere to the vessel wall once injured and aggregate with in themselves in order to seal the breech with platelet plug(primary haemostasis) and also in conversion of fibrinogen to fibrin strands mediated via thrombin to reinforce the platelet plug(secondary haemostasis).

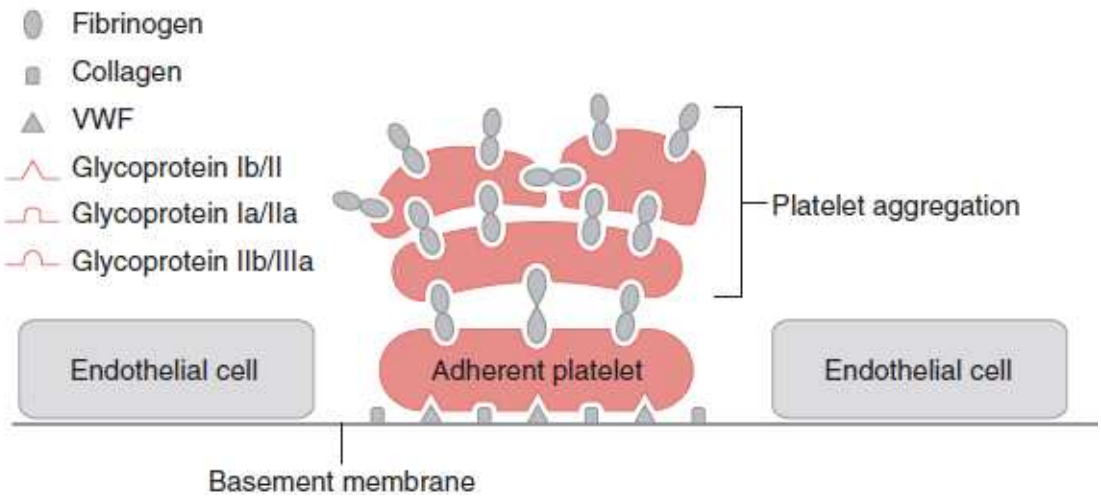
Platelet adhesion:

Vascular injury results in exposure of sub endothelial collagen and VWF. Clotting mechanisms are activated once factor vii comes in contact with the exposed collagen and tissue factor. Platelets also react by attaching to subendothelial collagen and VWF via glycoprotein receptors namely GPIa/IIa and GPIb/ix respectively present in the surface platelets. This process is referred to as adhesion. This results in release of platelet granules and fibrinogen and VWF high affinity receptor GPIIb[67,68].



Platelet aggregation:

The adherent platelet now attracts near by platelets by forming fibrinogen and VWF cross bridge. In addition activated platelet surface expose phosphatidyly residues for the vtamin k dependent clotting factors namely II,V,VII,X to act. The coagulation cascade occurs on the surface of platelet forming thrombin



Platelet indices:

They are markers for the early diagnosis of thrombo embolic diseases. Most of them were used as a surrogate marker for platelet activation

1. Mean platelet volume -MPV
2. Platelet distribution width- PDW
3. Platelet large cell ratio- P- LCR
4. Plateletocrit

Mean platelet volume:

Gives the average size of the platelets found in the blood. Calculated by automated counters by using optical light scatter techniques.

MPV : plateletcrit/number of platelets

Similar to the MCV calculated in red cell indices. The normal value range is 7 to 11 fl. It is influenced by addition of anticoagulants and delay in time from sampling to analysis. With EDTA 7.9% increase in 30 min to 13.4% increase after 24 hrs of sample collection. This could be minimised by using citrate tubes and standardizing time delay.

Larger platelets are younger more reactive and contains more thrombogenic factors. MPV is inversely proportional to the platelet count. In patients with severe thrombocytopenia less than 20,000 MPV was found to be more valuable marker of haemorrghic episode rather than the count.

Increase in MPV has been associated with peripheral immune destruction disease where the marrow response is good to release younger and larger platelets. Eg- inflammatory bowel disease, immune thrombocytopenic prpura, pre eclampsia.

Bernard soulier syndrome is associated with large platelet.

Lower MPV is associated with marrow disease

MPV has also been found to be increases in patients with pulmonary hypertension, stroke, myocardial infarction and diabetes patients.

Thrombocytopenia with low MPV- aplastic anemia.

Platelet distribution width:

Simple and specific marker for activation of coagulation.

Size of distribution curve in Fl at 20%level of peak. More reliable marker to distinguish relative thrombocytosis from increase due to myeloproliferative disorders.

Normal value range- 11to 18

Other less commonly used indices are mean platelet component and mean platelet mass used to detect platelet activation.

Markers of platelet activation:

Increase in MPV and PDW are suggested as they signify platelet swelling and pseudopodia formation.

PULMONARY HYPERTENSION – ROLE OF PLATELETS

Pulmonary artery hypertension and platelet are related and it has been proved in various clinical trials. Platelet activation is seen in pulmonary arterial hypertension but whether the platelet activation is seen in other etiological factors leading to pulmonary hypertension is less well studied[69]. Platelet abnormalities leads to platelet activation and it releases various mediators which leads to progression of pulmonary hypertension. Once the platelets are activated, they cause thrombotic obstruction of the pulmonary arteries which increases the pulmonary artery pressure and as well as the vessels undergo remodelling in a negative way to further worsen the clinical condition of pulmonary hypertension. Whether the platelets are abnormally activated in pulmonary hypertension or the platelets activation causes pulmonary hypertension is still unclear. Anyhow, activated platelets worsen the clinical scenario of the pulmonary hypertension.

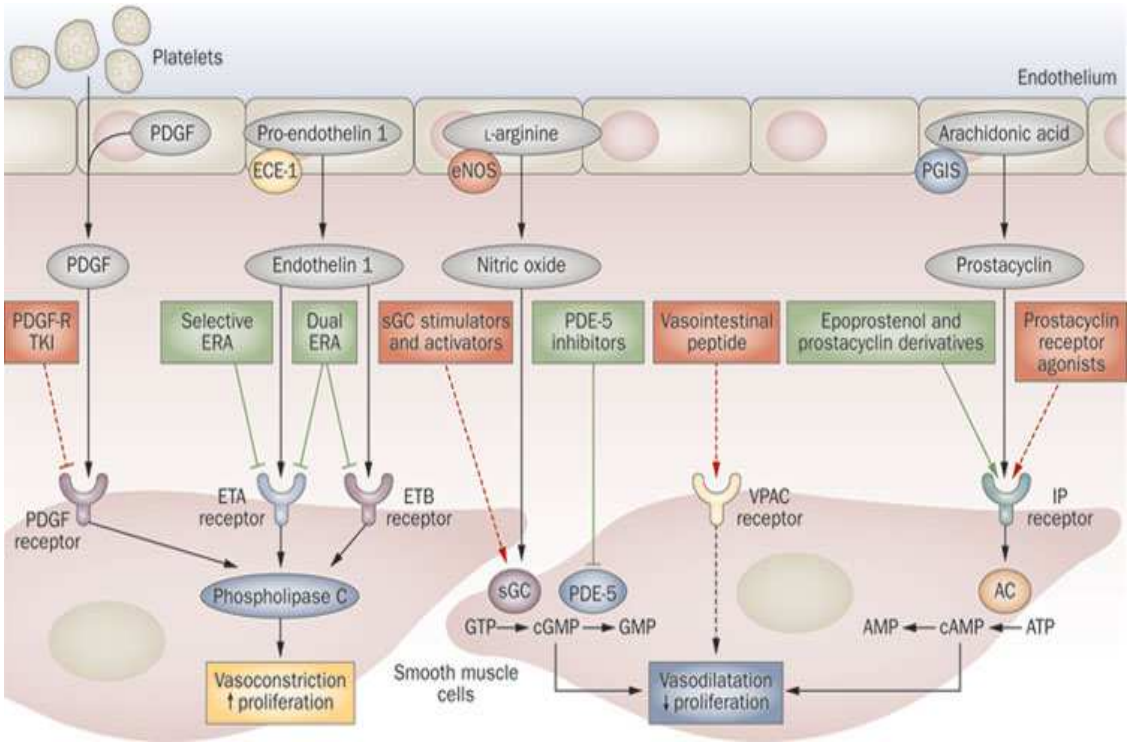
These platelets when they travel along the pulmonary vasculature in pulmonary arterial hypertension, they contribute to thrombin and clot along the vessels[70]. They also release their mediators like serotonin and platelet derived growth factors which causes smooth muscle cell proliferation and vessel medial hypertrophy leading to occlusion of the vessel and thereby increasing the chances of worsening pulmonary

hypertension. Studies have shown that, the platelets in pulmonary hypertension have lesser serotonin levels compared to normal individuals indicating that these abnormally activated platelets are degranulated and released the serotonins.

Abnormally activated platelets are diagnosed by the Mean Platelet Volume (MPV). The MPV is increased in the pulmonary hypertension. It is very high in Pulmonary arterial hypertension and left heart failure leading to pulmonary hypertension than other aetiologies like right heart failure, obstructive sleep apnoea etc leading to pulmonary hypertension.

Large platelets are highly reactive and more thrombotic than normal one. These large platelets are increased in pulmonary arterial hypertension. They also contain more dense granules and high levels of serotonin and hence release these by products in higher amount. These large platelets also causes increased platelet aggregating activity which further worsen the condition[71].

Increased mean platelet volume means increased platelet activity. However the increase in mean platelet volume does not correlate with the total thrombocyte count. So it indicates that there is a primary abnormality rather than a response to total thrombocyte number.



In pulmonary hypertension due to COPD, LVF etc there is no primary pathology in pulmonary arterial system but however when the disease progresses further it causesarterial vasoconstrictive response and arteriole changes which are partly because of the platelet activation. Hence the mean platelet volume is increased in these aetiology leading to pulmonary hypertension. But platelet activation directly is not related to the disease. So the mean platelet volume raise is not as high as those cases with primary pulmonary arterial hypertension but there is a definitive raise in the mean platelet volume. All these findings implies that platelet activation is seen in all causes of pulmonary hypertension

either directly or indirectly and it also aid in the progression of the disease in spite of it is not the cause for it.

Systemic hypoxaemia and metabolic acidosis stimulates platelet activation in COPD leading to pulmonary hypertension. Studies shown that inducing hypoxemia in healthy individuals does not activate platelets whereas, patients with pulmonary hypertension and hypoxemia in COPD showed marked increase in mean platelet volume and altered platelet morphology with more number of large platelets. These results indicate that platelet activation occurs in pulmonary hypertension of all aetiologies and not only with the pulmonary hypertension.

Increased shear forces of platelets in pulmonary vascular bed in pulmonary hypertension of any cause, leads to activation of platelets, changing the antithrombotic properties of vascular endothelium and increased vessel wall and platelets interactions.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

Source of data:

Patients admitted in Rajiv Gandhi Government General hospital who on evaluation diagnosed to have pulmonary hypertension using echocardiographic evidence are explained about the study in their own language. Patients willing to participate are included into the study after getting consent for the study.

Study design:

Observational study

Study centre:

Institute of internal medicine

Rajiv Gandhi Government General hospital, Chennai -600003

Duration of study:

6 months from April 2015 to September 2015

Inclusion criteria:

All patients with echocardiographic evidence of pulmonary hypertension age more than 18 yrs willing to participate in the study were included.

Exclusion criteria:

- Patients already under treatment of anti coagulants
- Presence of liver disease
- Haematological malignancies
- Platelet function disorders
- Fevers causing thrombocytopenia
- Pregnant patients
- Renal failure patients on haemodialysis

Sample size:

104 patients were included in the study

Data collection method:

Patients admitted with symptoms, signs suggestive of pulmonary hypertension on evaluation with echocardiogram diagnosed to have pulmonary hypertension are subjected to thorough

1. History of presenting illness
2. Past history
3. Clinical examination
4. Systemic examination
5. Investigations:

- Complete blood count done by automated analyser
- Bleeding time
- Clotting time
- Peripheral smear
- ECG
- Chest x ray
- Echocardiogram done by cardiologist.

METHODOLOGY:

Presenting complaints:

A detailed history of presenting illness collected to functionally classify the severity of pulmonary hypertension using WHO scales.

Main complaints are,

- Breathlessness- onset, duration , aggravating , relieving factors, associated symptoms, orthopnoea, PND and grade of breathlessness
- Chest pain- site of pain, radiation, onset, duration , aggravating , relieving factors, associated symptoms
- Abdomen distension
- Pedal odema
- Jaundice
- Bleeding manifestation

Past history:

Diabetes mellitus , hypertension, coronary heart disease, stroke , renal disease

General examination : pallor, icterus, cyanosis, clubbing, pedal odema, lymph node, jugular venous pulse

Systemic examination :

Cardiovascular system: palpable p2, Early systolic click, Left Parasternal heave, JVP with prominent a, v wave, Holosystolic murmur of TR, Diastolic murmur of pulmonary regurgitation

Abdomen:

Hepatomegaly, pulsatile liver, aacities

Respiratory system:

Features of volume loss, coarse leathery crackles, hyperinflated lung

Investigations:

Complete blood count:

Around 2 ml of intravenous sample obtained and collected in EDTA test tubes and care taken to process all the collected sample in automated analyser with one hour of collection in order to avoid the

effect of time on the calculated MPV and to obtain comparable sample. The automated analyser uses optical light scatter method to access the volume of the cells. RBC indices, WBC with differential count , platelet indices are all obtained at the same time.

Bleeding time:

Clotting time

Peripheral smear:

ECG: RVH with strain, right axis deviation, complete or incomplete RBBB, ratio of R wave to S wave more than 1 in lead V1. P pulmonale in lead II

Chest X ray:

Echocardiogram:

1.MEASUREMENT OF TR JET VELOCITY

2.ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

3.ASSESSMENT OF LEFT VENTRICULAR FUNCTION

OBSERVATION

AND

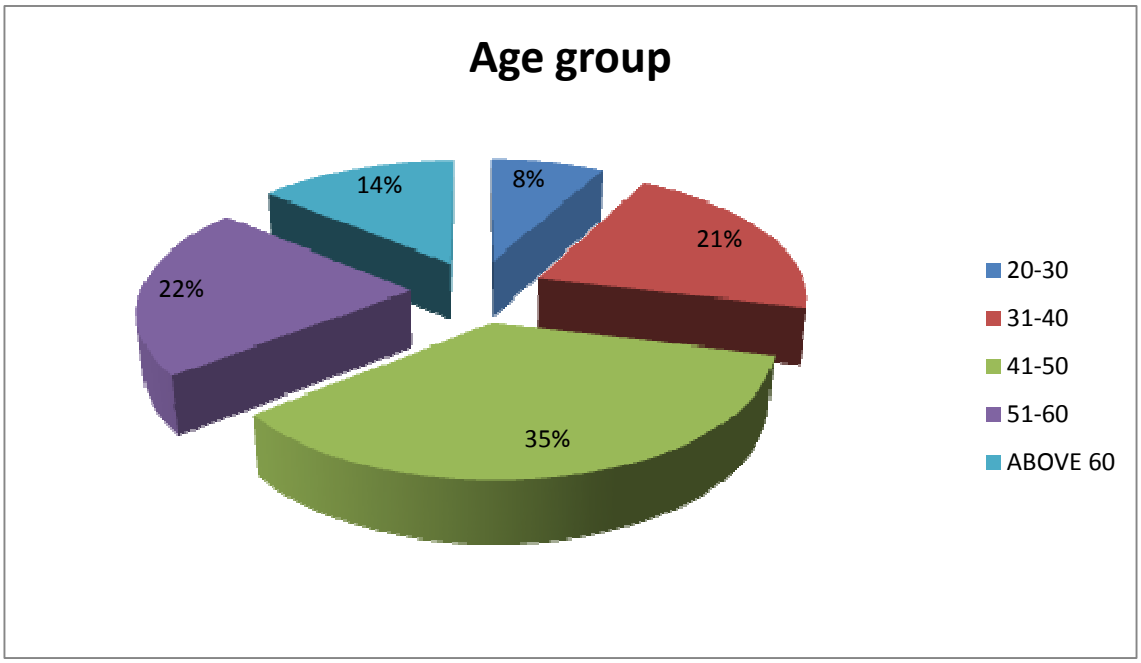
RESULTS

OBSERVATION AND RESULTS

In our study 104 patients were enrolled out of them 37(36.5%) belong to the age group 41 – 50 years. Least number of patients belong to the age group 20 – 30 years.

AGE GROUP

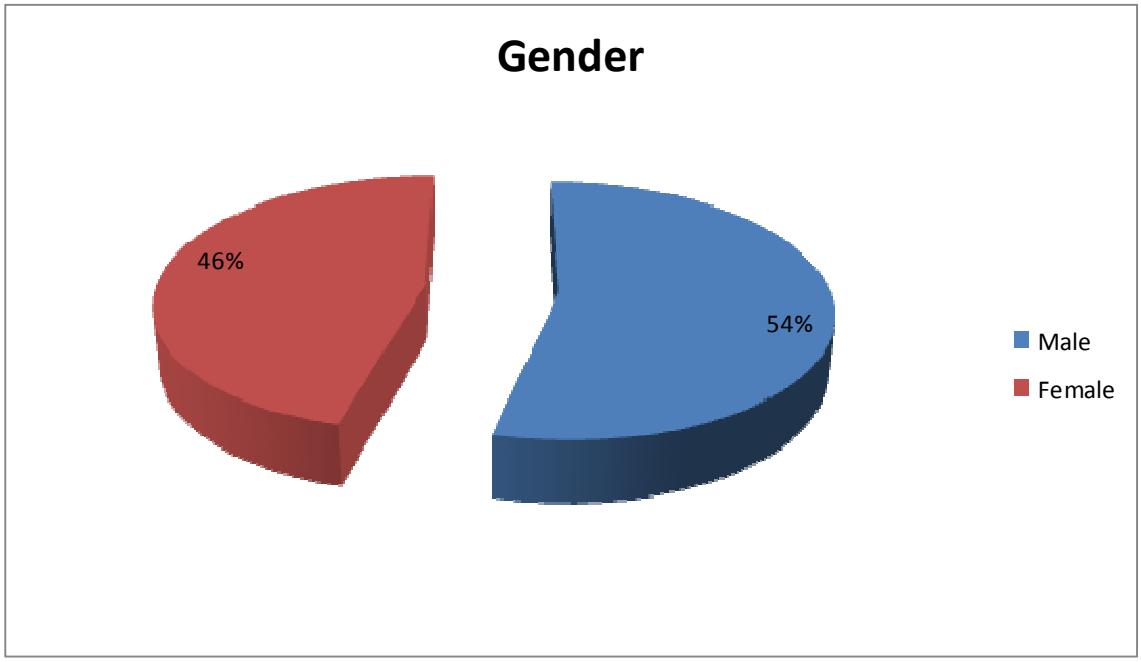
AGE GROUP	NO. OF PATIENTS	PERCENT
20-30	8	7.7
31-40	22	21.2
41-50	37	35.6
51-60	23	22.1
ABOVE 60	14	13.5
Total	104	100.0

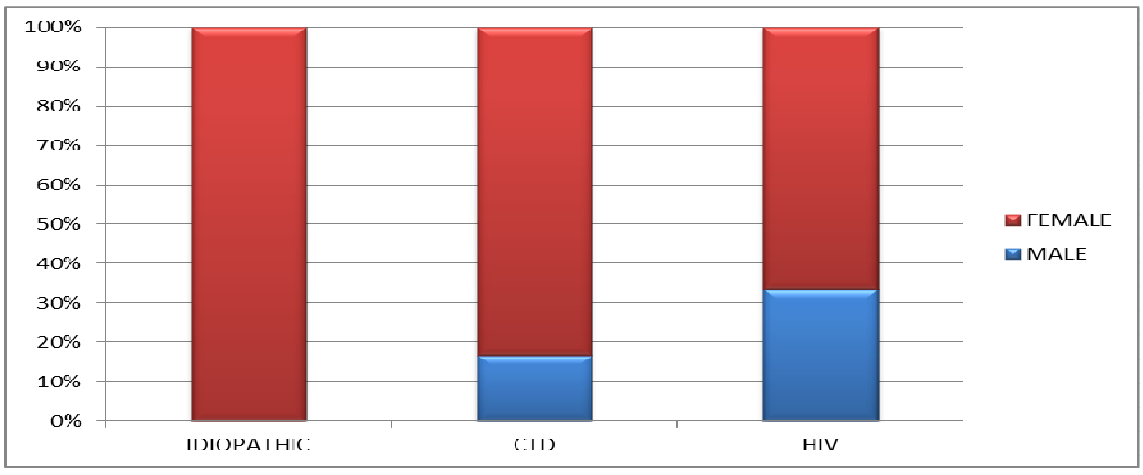


Gender

GENDER	PATIENT	PERCENT
MALE	56	53.8
FEMALE	48	46.2
TOTAL	104	100.0

In this study, male and female incidence are almost equal with incidence of male being slightly higher.



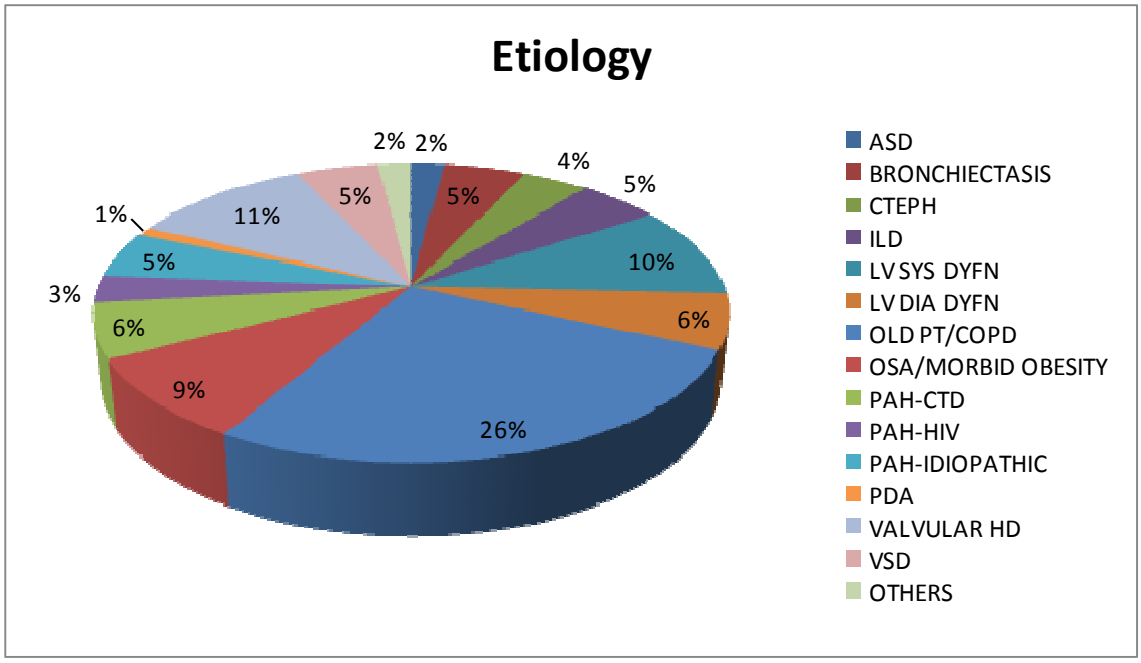


Pulmonary Arterial Hypertension:Among patients with PAH idiopathic causes are common. Seen mostly in females.

Aetiology:

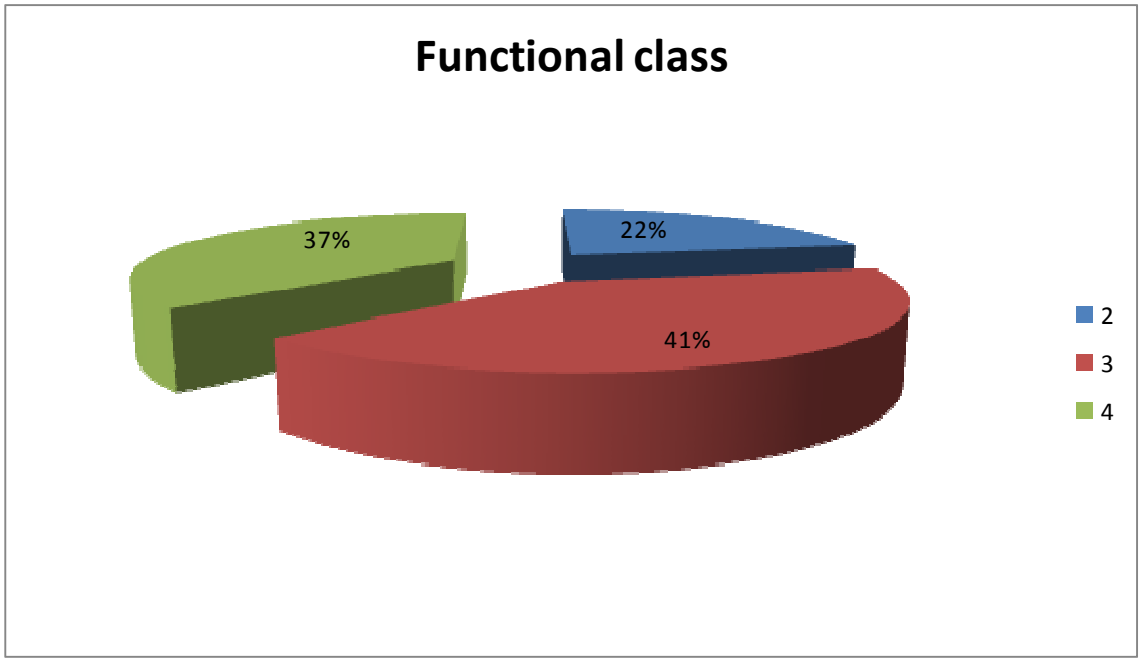
Out of 104 patients, 27 patients due to old pulmonary tuberculosis and COPD form the major cause.

ETIOLOGY	NO. OF PATIENTS	PERCENT
ASD	2	1.92
BRONCHIECTASIS	5	4.81
CHEST DEFORMITIES	3	2.88
CTEPH	4	3.85
ILD	5	4.81
LV SYS DYFN	10	9.62
LV DIA DYFN	6	5.77
OLD PT/COPD	27	25.96
OSA/MORBID OBESITY	9	8.65
OTHERS	2	1.92
PAH-CTD	6	5.77
PAH-HIV	3	2.88
PAH-IDIOPATHIC	5	4.81
PDA	1	0.96
VALVULAR HD	11	10.58
VSD	5	4.81
TOTAL	104	100


Etiology
2%
2%
4%
5%
5%
5%
1%
11%
10%
5%
3%
6%
6%
9%
26%
ASD
BRONCHIECTASIS
CTEPH
ILD
LV SYS DYFN
LV DIA DYFN
OLD PT/COPD
OSA/MORBID OBESITY
PAH-CTD
PAH-HIV
PAH-IDIOPATHIC
PDA
VALVULAR HD
VSD
OTHERS

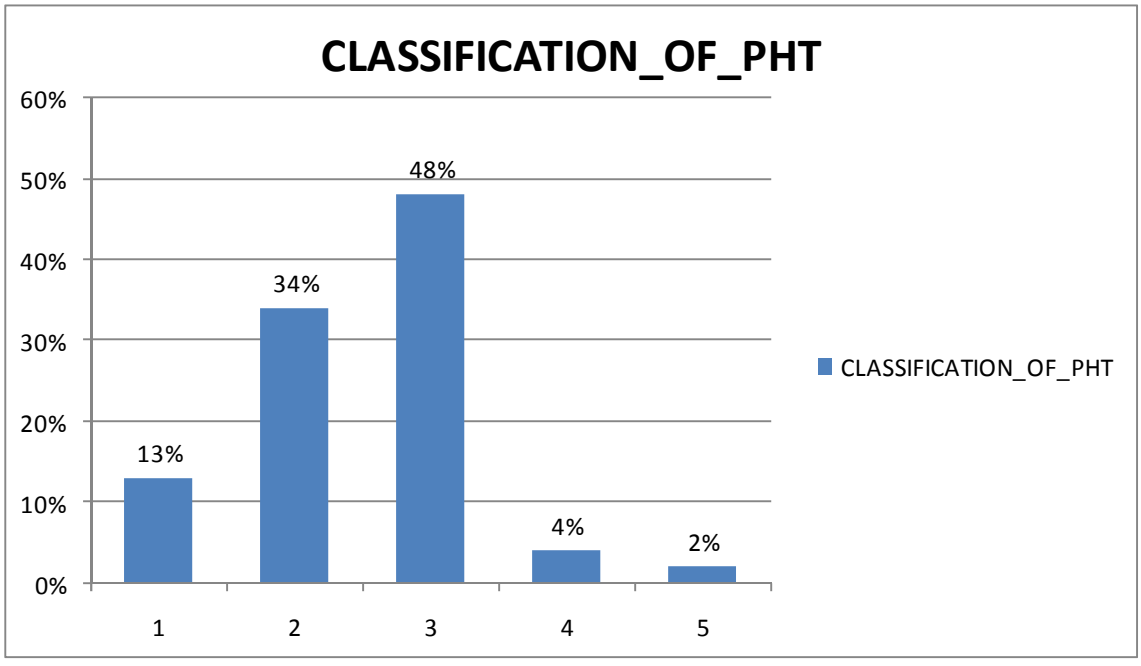
WHO functional class: Most of the patients admitted 43(41.3%) where in functional class 3.

Functional class	No. Of Patient	Percent
Class I	0	0
Class II	23	22.1
Class III	43	41.3
Class IV	38	36.5
Total	104	100.0



Classification of Pulmonary Hypertension

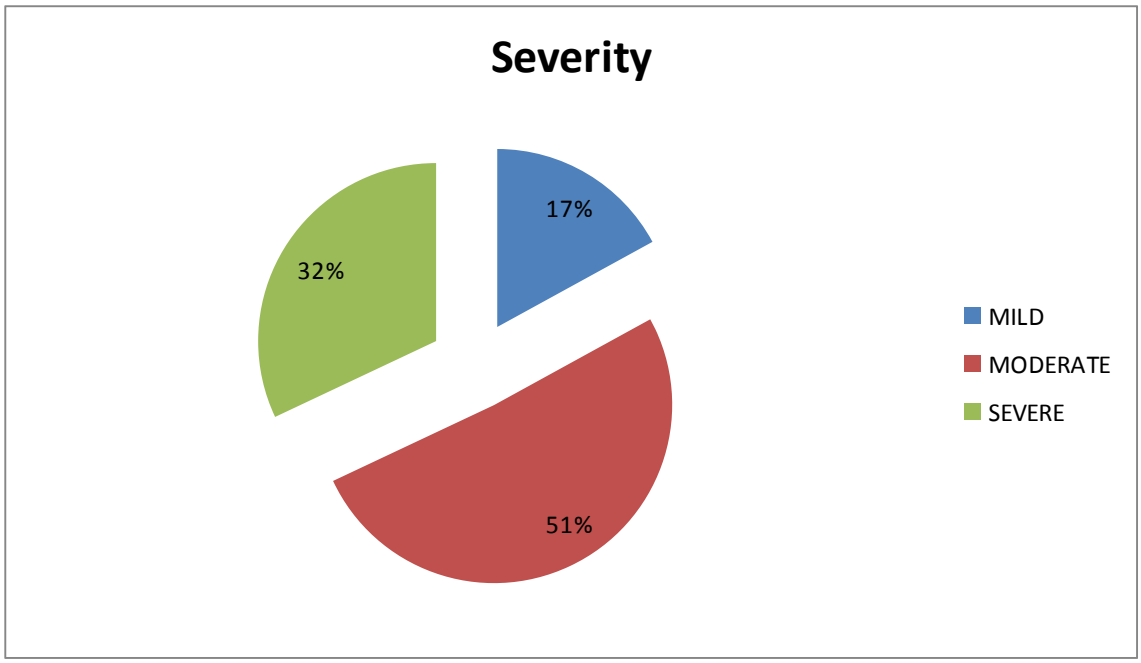
Groups	No. Of Patients	Percent
I	13	12.5
II	35	33.7
III	50	48.1
IV	4	3.8
V	2	1.9
Total	104	100.0



SEVERITY GRADE OF PULMONARY HYPERTENSION:

graded as mild, moderate and severe depending upon mPAP

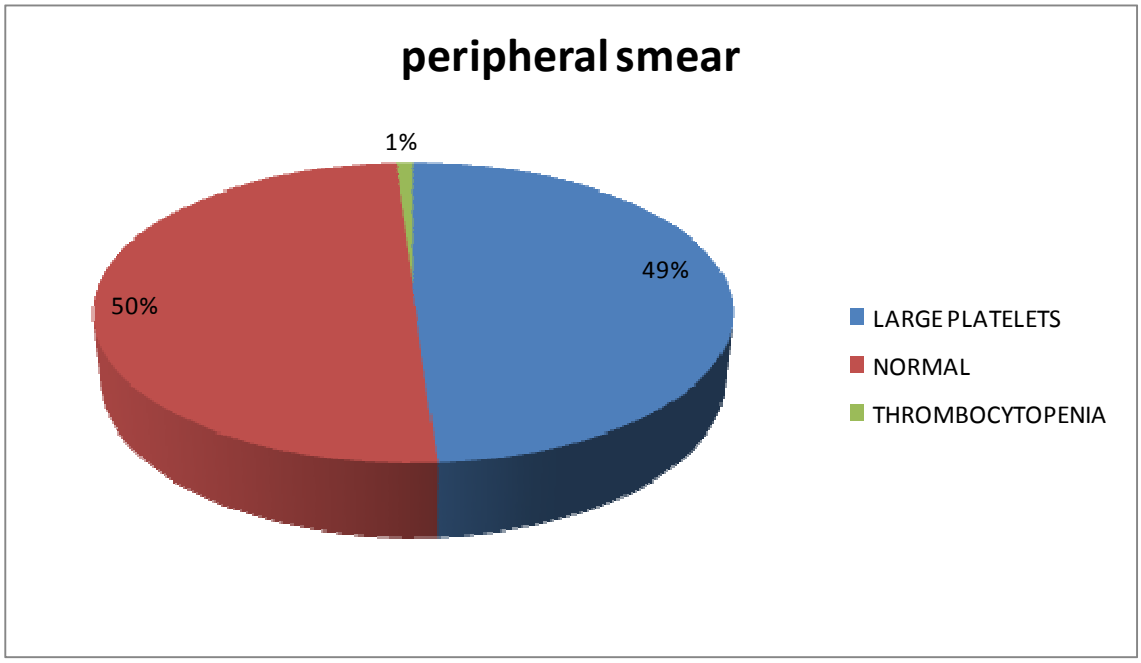
Severity	No. of patients	Percent
MILD	18	17.3
MODERATE	53	51.0
SEVERE	33	31.7
Total	104	100.0



PERIPHERAL SMEAR:

Most of the patients 52 (50%) had normal smear

PERIPHERAL SMEAR	NO. OF PATIENTS	PERCENT
LARGE PLATELETS	51	49.0
NORMAL	52	50.0
THROMBOCYTOPENIA	1	1.0
TOTAL	104	100.0



VALVES:

Mild TR seen 34(32.7%) of the patients.

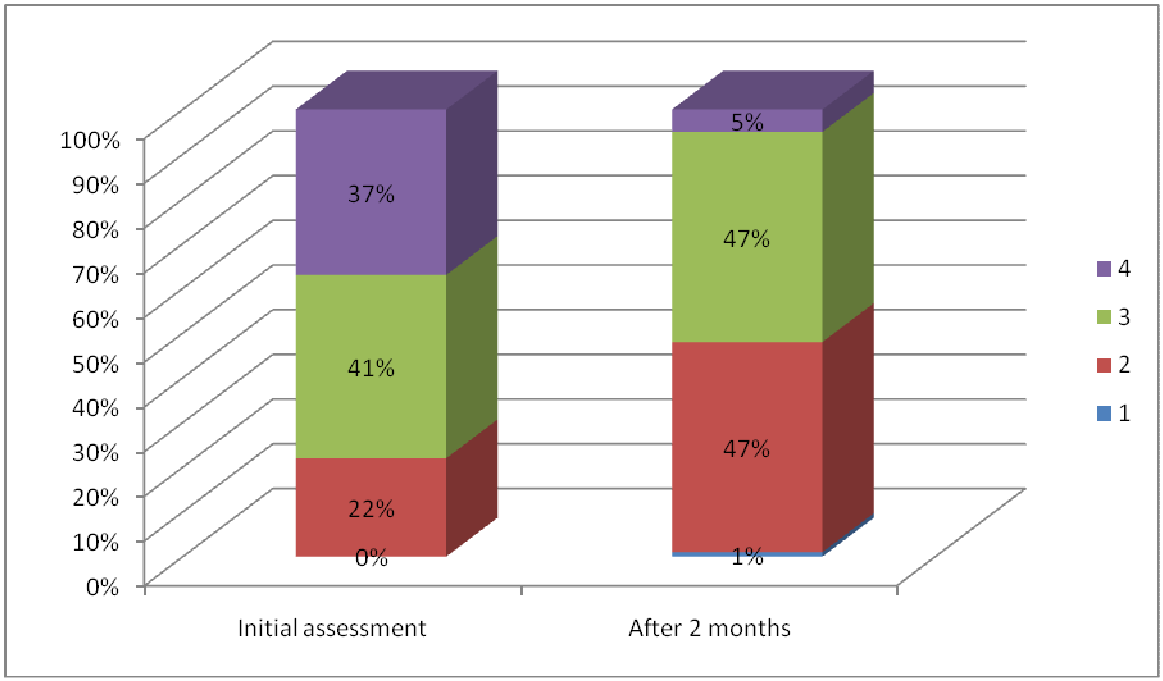
VALVES	NO OF PATIENTS	PERCENT
MILD MR	14	13.5
MILD TR	34	32.7
MODERATE MR	9	8.7
MS MODERATE	5	4.8
MS/MR	2	1.9
NORMAL	28	30.8
SEVERE MS	5	1.0
TR MODERATE	1	1.0
VSD MILD MR	2	1.9
VSD MILD TR	3	2.9
TOTAL	104	100.0

REVIEW AFTER 2 MONTHS OF TREATMENT:

All enrolled patients are given treatment according to the group which they belong to and review after 2 months. The effect of treatment assessed in terms of functional class, hemogram and echo

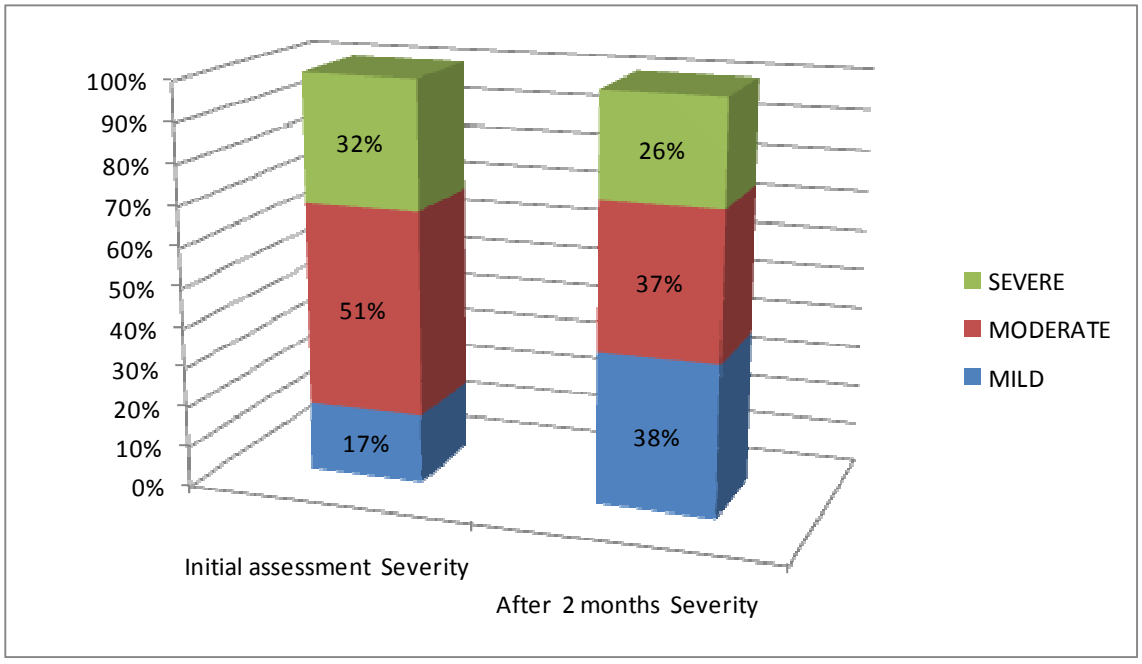
Who functional class:

Functional class				
	1	2.00	3.00	4.00
Initial assessment	0(0.00%)	23 (22.1%)	43(41.3%)	38(36.5%)
After 2 months	1 (1.1%)	44 (47.3%)	44 (47.3%)	4 (4.3%)



Severity of pulmonary hypertension:

Severity	Initial assessment		After 2 months of treatment	
Grade	No of patients	Percent	No of patients	Percent
MILD	18	17.3	35	38
MODERATE	53	51.0	34	37
SEVERE	33	31.7	24	26
Total	104	100.0	93	100

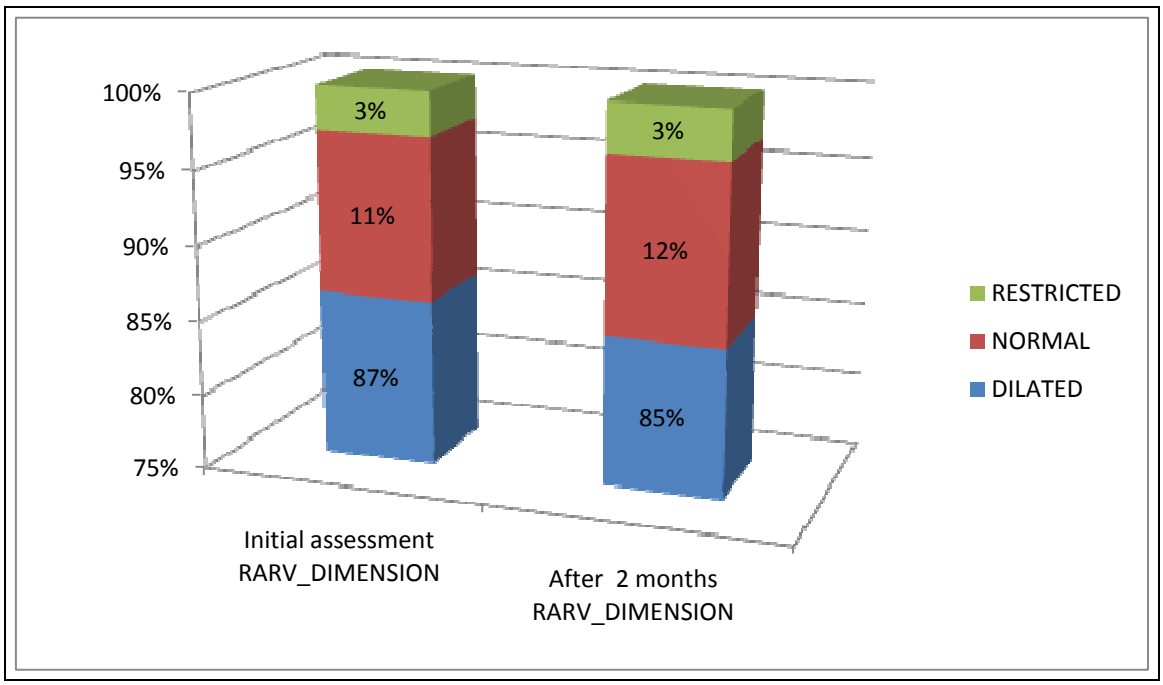


With treatment 51% patients with moderate PHT has reduced to 37%

RA/RV DIMENSION:

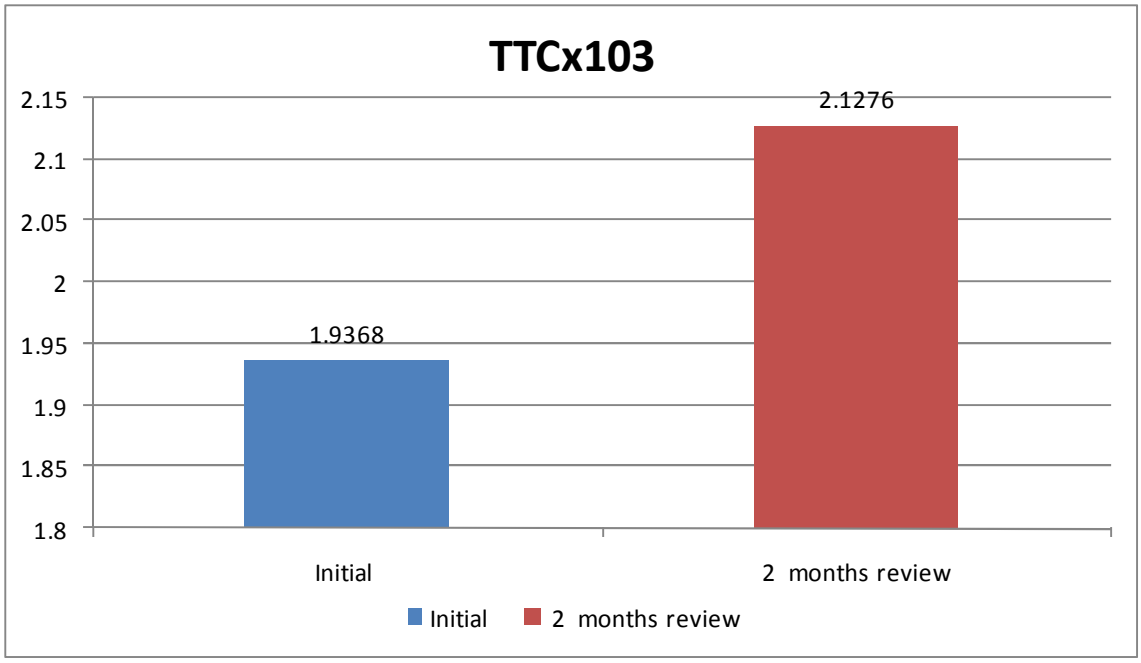
With treatment there was no significant change in dimensions of RA and RV

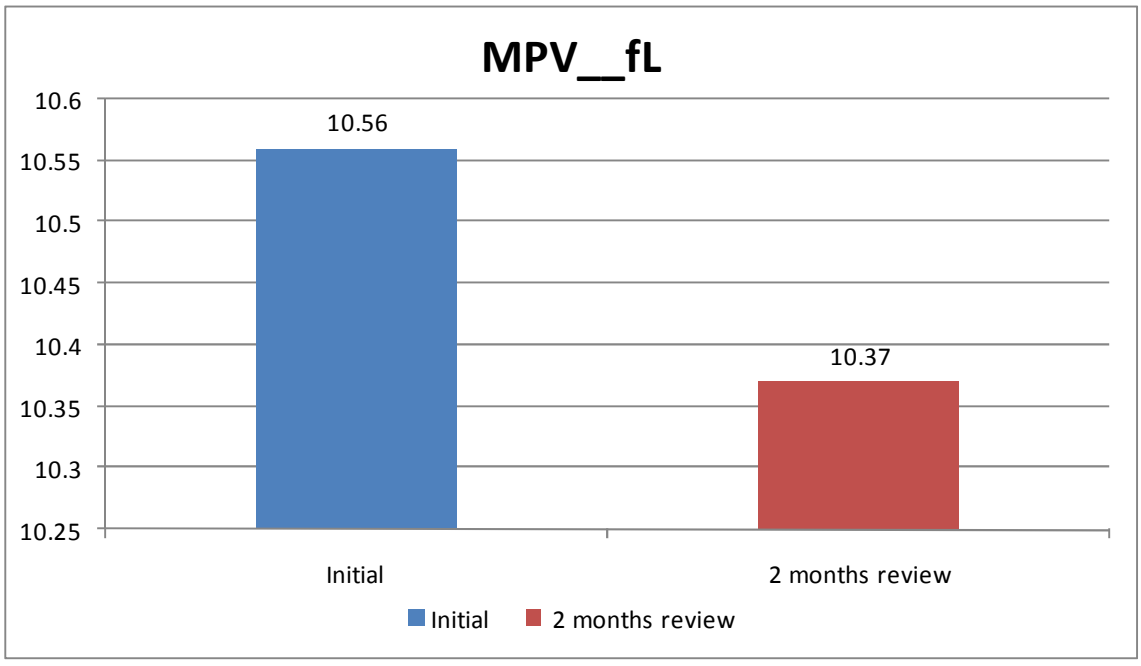
RA/RV DIMENSION	Initial assessment		After 2 months	
	No of patients	Percent	No of patients	Percent
DILATED	90	86.5	79	84%
NORMAL	11	10.6	11	12%
RESTRICTED	3	2.9	3	3%
Total	104	100.0	93	100

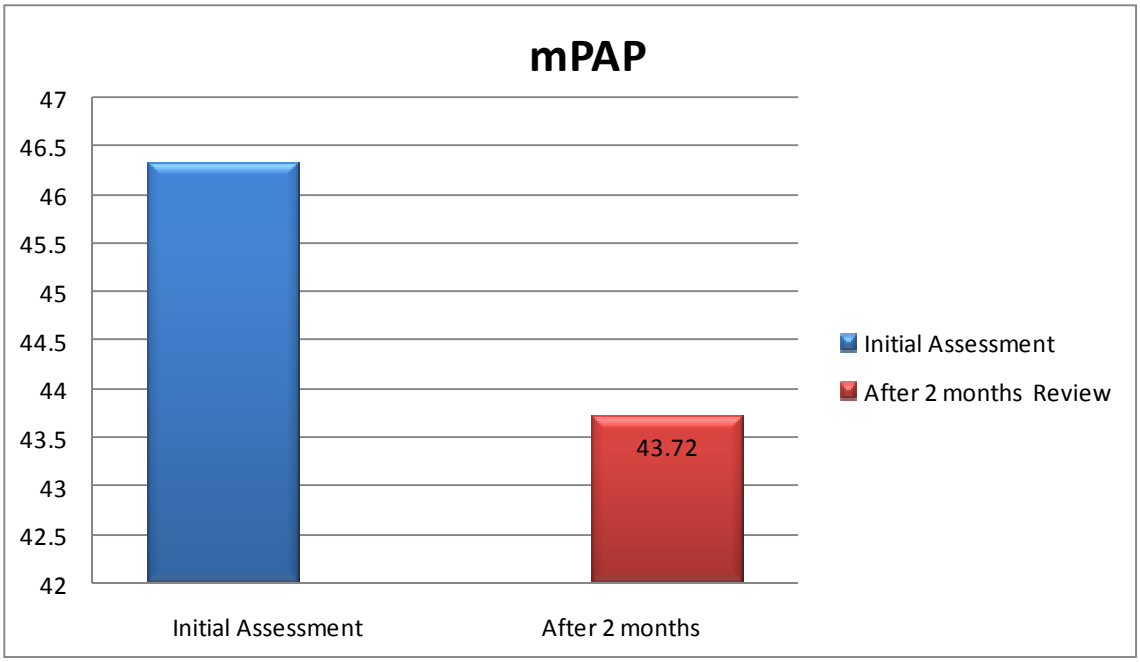


STATISTICAL ANALYSIS WITH PAIRED T TEST:

Paired Samples Statistics					
	Mean	N	Std.	Std.	
TTCx103	1.9368	93	0.44116	0.04575	
TTCx1031	2.1276	93	0.4334	0.04494	P<0.001
MPV__fL	10.5631	93	0.61704	0.06398	
MPV_fL	10.3742	93	0.55284	0.05733	P<0.001
PDW	16.7978	93	1.73387	0.17979	
PDW1	16.9054	93	1.62256	0.16825	P>0.05
PLCR	27.5108	93	3.68751	0.38238	
PLCR1	26.8817	93	3.20614	0.33246	P<0.001
mpap_0#61xPSAP2	46.3376	93	9.84252	1.02062	
mPAP	43.7225	93	9.60185	0.99567	P<0.001
TAPSE	15.5054	93	1.65256	0.17136	
TAPSE1	15.9355	93	1.64056	0.17012	P<0.001
EF_	56.6667	93	9.19396	0.95337	
EF	57.7957	93	6.75915	0.70089	P<0.05


TTCx103
2.15
2.1
2.05
2
1.95
1.9
1.85
1.8
1.9368
2.1276
Initial
2 months review
Initial
2 months review


MPV__fL
10.6
10.55
10.5
10.45
10.4
10.35
10.3
10.25
10.56
10.37
Initial
2 months review
Initial
2 months review



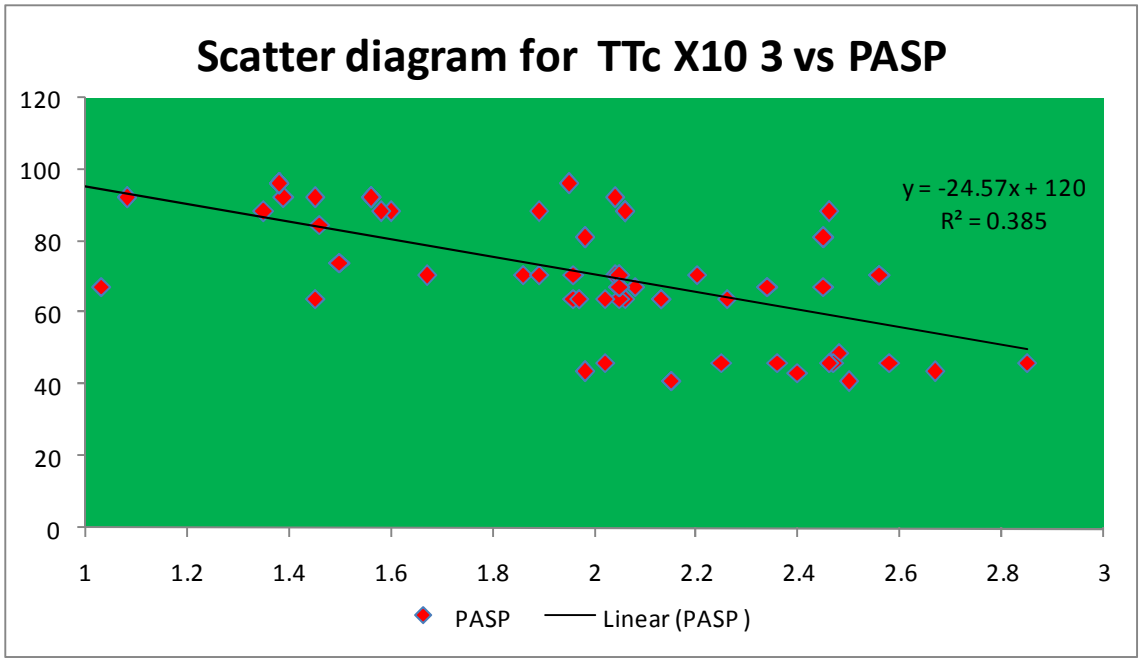
With treatment the thrombocyte count and the platelet indices are altered as the mPAP decrease with treatment.

CORRELATION OF TTC WITH ECHO PARAMETERS:

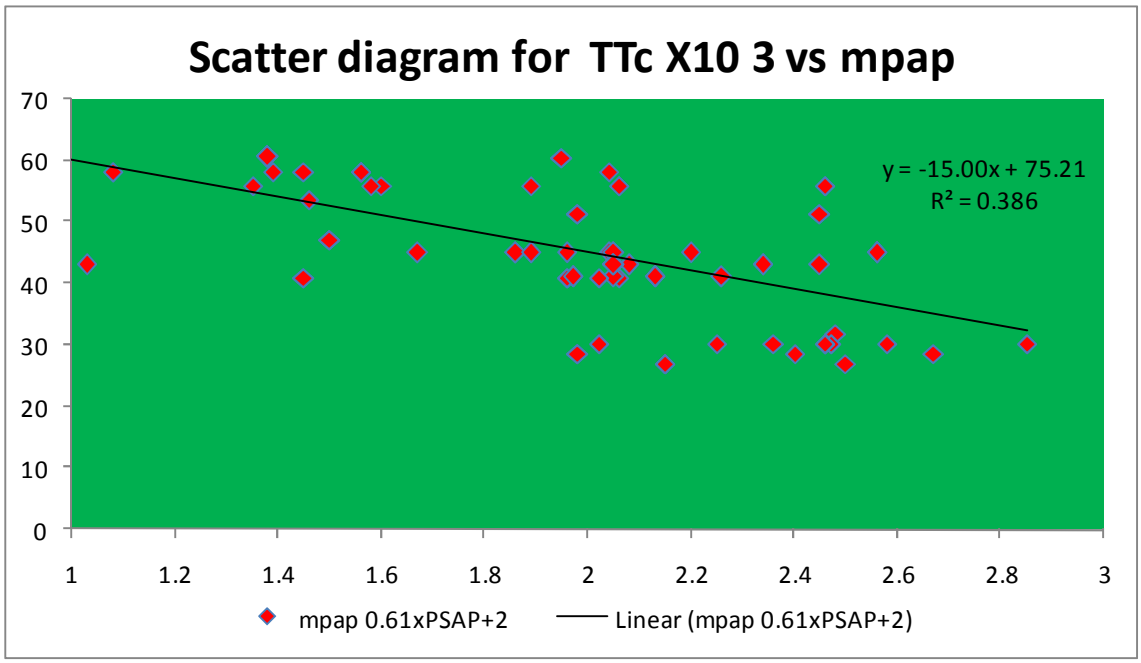
		PASP	mPAP	SYSTOLIC_FN	DIASTOLIC_FN	EF_	PERICARDIAL_EFFUSIONCLOT	severity
TTCx103	Pearson Correlation	-.621**	-.621**	.263**	-.052	-.176	-.259**	-.622**
	Sig. (2-tailed)	.000	.000	.007	.603	.074	.009	.000
	N	104	104	104	104	104	102	104

Correlation is significant at the 0.01 level (2-tailed).

Correlation is significant at the 0.05 level (2-tailed).

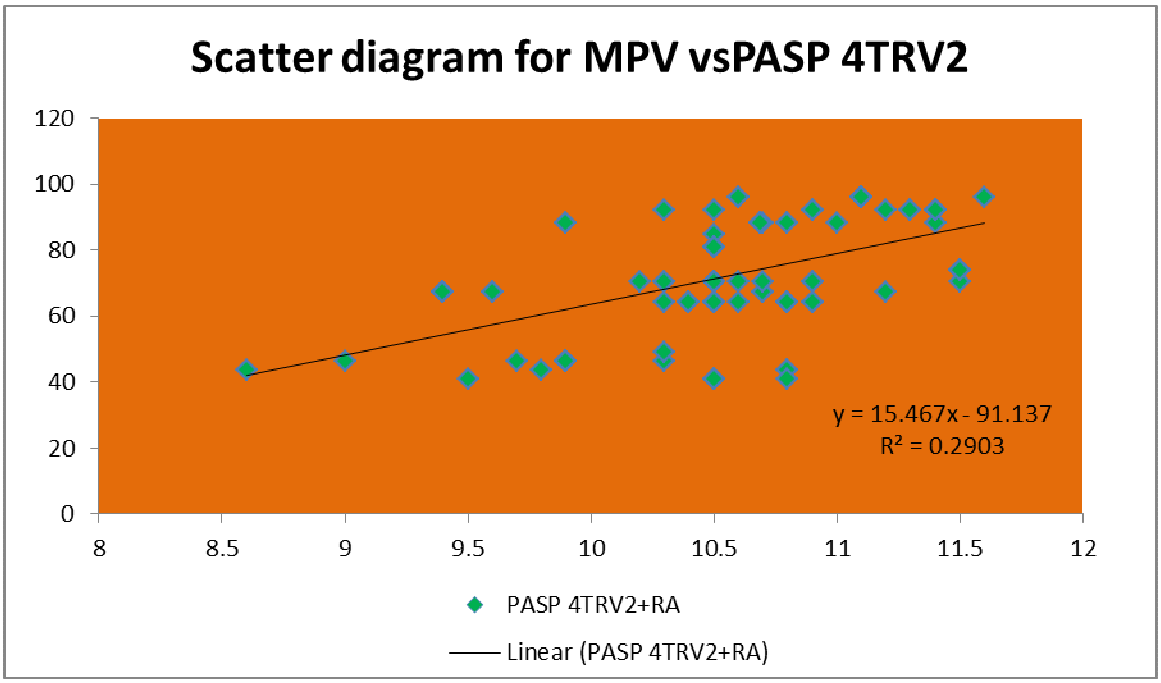


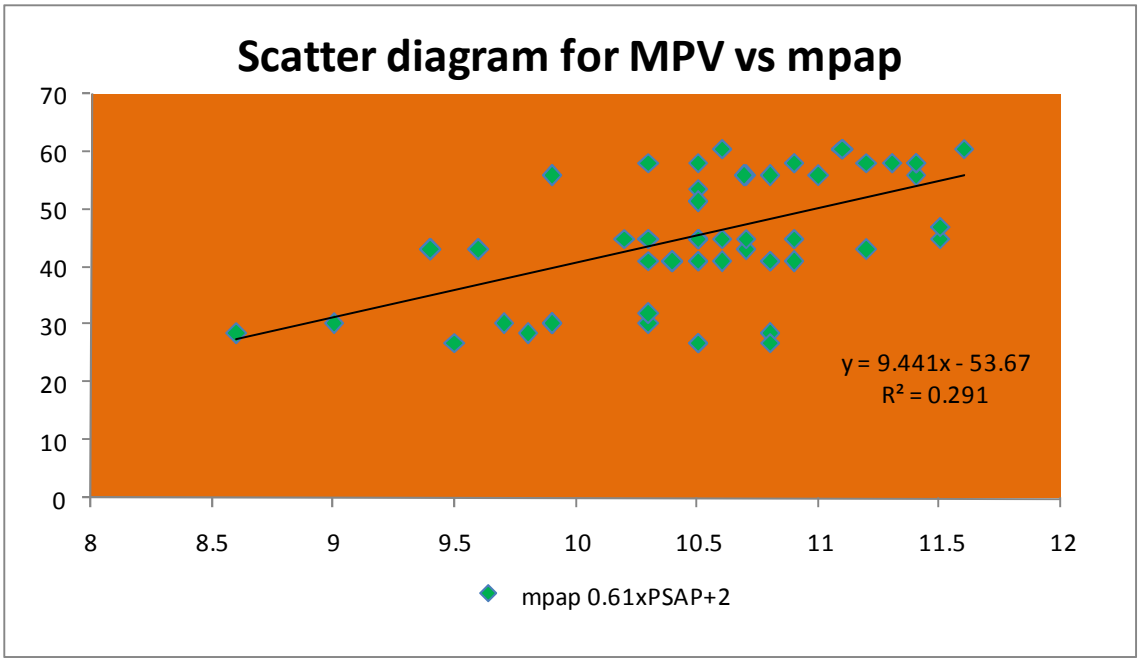
Thrombocyte count co relates with mPASP, as mPASP increase TTC decreases



CORRELATION OF MPV WITH ECHO PARAMETERS:

		PASP_4TRV2RA	mpap_0#61xPSAP2	SYSTOLIC_FN	DIASTOLIC_FN	EF_	severity
MPV__fL	Correlation Coefficient	.547**	.562**	-.314**	-.027	-.005	.547**
	Sig. (2-tailed)	.000	.000	.001	.786	.959	.000
	N	104	104	104	104	104	104

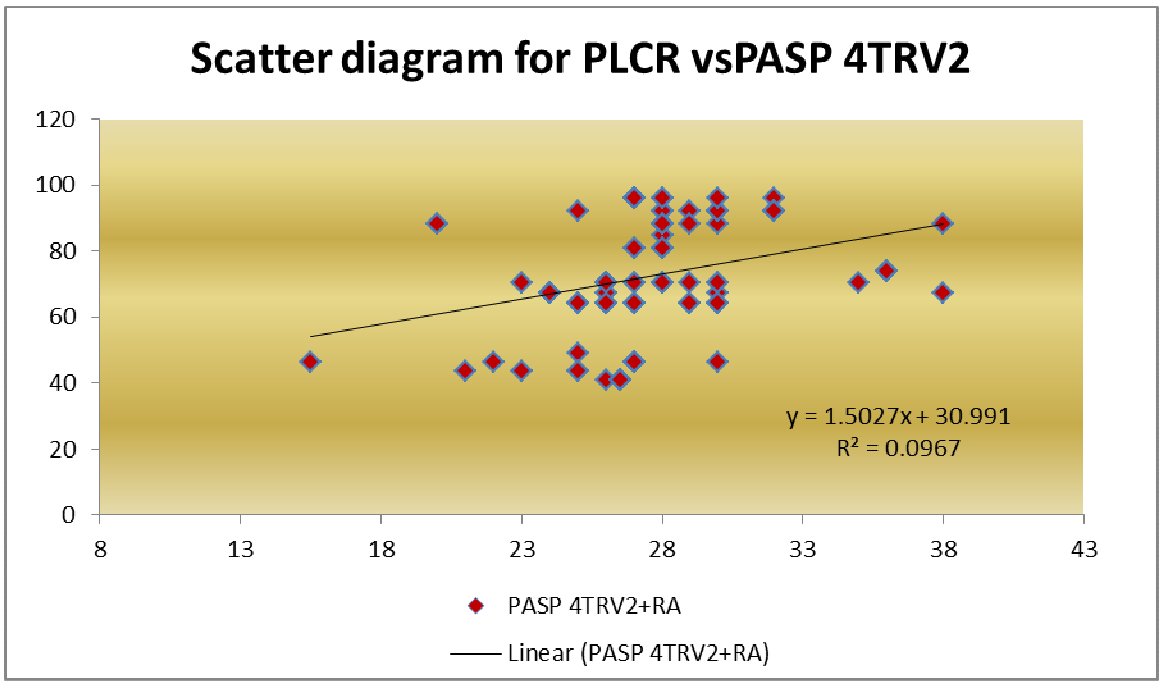


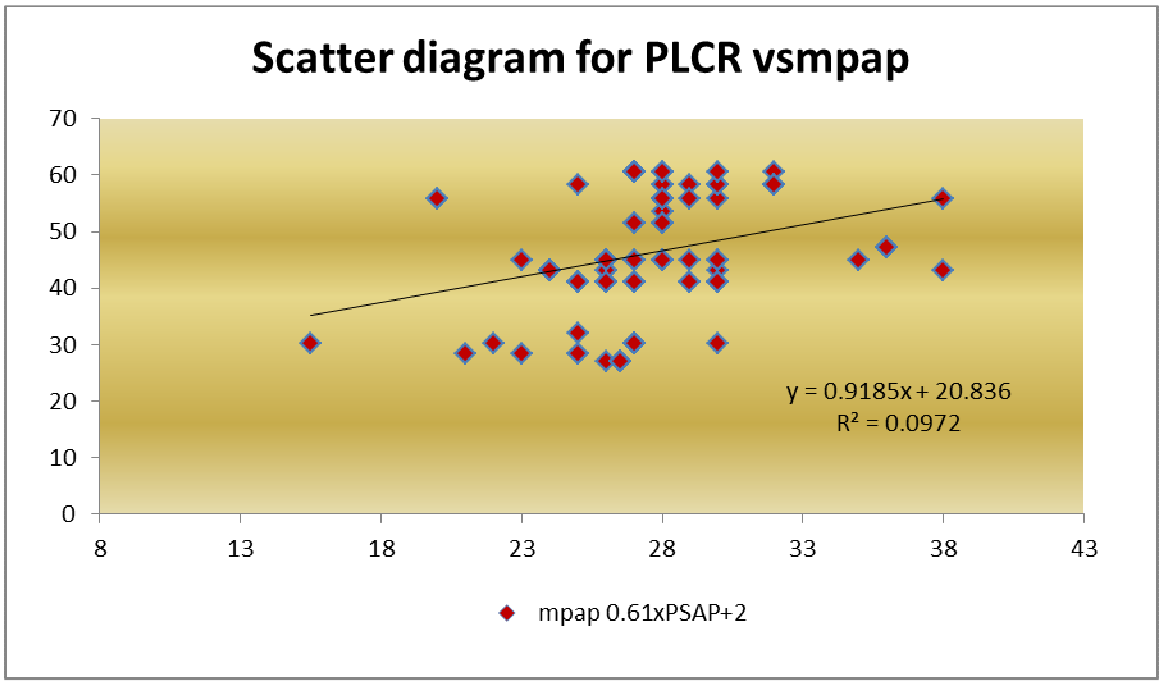


MPV has significant correlation with PASP, mPAP, severity of pulmonary hypertension. MPV also has correlation with left ventricular systolic function.

Correlation of P- LCR with echo parameters

		PASP_4TRV2RA	mpap_0#61xPSAP2	SYSTOLIC_FN	DIASTOLIC_FN	EF_	PERICARDIAL_EFFUSIONCLOT	severity
PLCR	Pearson Correlation	.311**	.312**	-.190	-.062	.157	.002	.282**
	Sig. (2-tailed)	.001	.001	.053	.532	.112	.983	.004
	N	104	104	104	104	104	102	104





P-LCR correlates with PASP, mPAP, Severity of pulmonary hypertension.

Wilcoxon Signed Ranks Test:

	FUNCTIONAL_CLASS1 - FUNCTIONAL_CLASS	RARV_DIMENSION1 - RARV_DIMENSION	PERICARDIAL_EFFUSIONCLOT1 - PERICARDIAL_EFFUSIONCLOT	SEVERITY1 - severity
Z	-7.488[b]	-1.414[b]	-3.354[b]	-4.914[b]
P VALUE	.000	.157	.001	.000

With treatment the functional , severity of pulmonary hypertension and poor prognostic factors like pericardial effusiona an dclot improves without significant improvement in right atrial and ventricular dimensions.

DISCUSSION

DISCUSSION

In our study we collected data of all newly diagnosed cases of pulmonary hypertension admitted in our hospital. Proper consent obtained after explaining the nature of study and investigations done. Patients willing to participate and accepted to come for review were enrolled in the study. All the enrolled patients were subjected to clinical history taking, general and systemic examination. Functional class accessed according to WHO grade used for pulmonary hypertension. Then blood for CBC and peripheral smear obtained and sent to process within 1 hour of collection. Bleeding and clotting time calculated. After taking ECG and chest X- ray, echocardiogram was done by cardiologist to access the pulmonary artery pressure using tricuspid regurgitation jet velocity there by pulmonary systolic artery pressure and mean pulmonary artery pressure were calculated. Right atrial and ventricular dimension were calculated. Tricuspid annular plane systolic excursion(TAPSE) value is calculated there by right ventricular dysfunction is assessed. Left ventricular systolic and diastolic function accessed. Ejection fraction calculated. Condition of valves were seen. Presence of pericardial effusion or clot were noted.

Aetiology:

In our study in 104 patients divided into 5 groups , pulmonary hypertension due to chronic lung disease was found to be the commonest cause. It accounts for 50 (48%) of total patients. This prevalence is in accordance to the previous studies in Indian population, while in western countries pulmonary hypertension due to cardiac causes forms the most common cause.

Among the chronic lung diseases causing pulmonary hypertension, COPD and old pulmonary tuberculosis form the most common cause accounting for 20%. May be due to increased prevalence of smoking and pulmonary tuberculosis in our population.

The second most common cause of pulmonary hypertension among 5 groups is due to cardiac diseases accounting for 34%. Among them valvular diseases forms the major cause followed by systolic dysfunction. There could be significant overlap between group 2 and group 3 due the presence of similar risk factors and pathogenic mechanisms for both.

Age:

Most common age at presentation being 41 to 50 yrs where 37 patients has been diagnosed. Incidence is very low in younger population, in this age congenital and valvular heart disease predominates.

Sex:

In our study, prevalence of disease is more common in males 56(53%), as opposed to greater prevalence in female population may be due to more number of COPD cases occurring in males due to smoking. But the prevalence of pulmonary arterial hypertension due to idiopathic causes predominates in females. Occurrence of connective tissue disorder leading to pulmonary hypertension is also seen in female population.

Functional class:

Most of the patients admitted and diagnosed were having WHO functional class 3 accounting for 43 (41%), as patients with milder functional class are not seeking medical attention or not getting hospitalised for evaluation and treatment.

Severity of pulmonary hypertension:

Most of the patients diagnosed were having moderate degree of pulmonary hypertension . 53 patients had mPAP between 41 to 55 mmhg. This may be due to delay in early diagnosis of pulmonary hypertension. A delay of 2 to 5 years in diagnosis has been documented in various pulmonary hypertension registries.

Peripheral smear in PT:

Half of the patients with pulmonary hypertension had a normal peripheral smear study. Almost all patients with pulmonary arterial hypertension showed large platelets as compared to other groups. Thrombocytopenia is not a regular association seen in pulmonary hypertension. But when present indicates poor prognosis as evidenced by H.weaver, European heart journal aug 1, 2013.

Valves in pulmonary hypertension:

Mild tricuspid regurgitation is commonly found valvular lesion. Its seen in 34 cases. Mild TR is mostly seen with moderate pulmonary hypertension causing Right atrial and right ventricular dilatation. As most patients presents late after development of moderate hypertension.

Bleeding time and clotting time:

There was no significant difference in bleeding or clotting time among the different groups of pulmonary hypertension. No relation was found with the severity of pulmonary hypertension.

Total thrombocyte count:

Is lower than normal in all groups of pulmonary hypertension ranging from 1.93 to 2.13x 10^3. patients with pulmonary arterial

hypertension had lower platelets than rest of the groups ranging from 1.67 to $1.84x10^3$. There is correlation between the platelet count and the PASP, mpAP and the severity of pulmonary hypertension. This study is in accordance to study by Guvenc et al, “comparing MPV values in various cause of pulmonary hypertension”, cardiology journal vol 19, 2012.

Platelet indices:

Mean platelet volume:

There is a inverse relation between the number of platelets and the volume and distribution of platelets. In our study mean platelet volume is increased in all causes of pulmonary hypertension especially with pulmonary artery hypertension ranging from 11. 3 to 10.9 owing to the increased activation of platelets. This is seen in accordance to the study done by Guvenc et al, comparing the MPV in different cause of pH.

Platelet distribution width:

As MPV, PDW is correlating with the severity of PH. It also correlates with the presence of systolic function as evidenced by Shu-ichi fajita et al in paltelet indices and left ventricular function.

RA and RV Dilataion:

Presence of RA and RV dilataion is associated with moderate to severe grades of pulmonary hypertension.

RV dysfunction:

As evidenced by decreased TAPSE of less than 16 is associated with severe pulmonary hypertension.

Review of patients 2 months after treatment:

Most of the patients were attending the OPD for procuring free medications and hence review had lesser drop outs. 11 patients could not be reviewed as either they expired or lost follow up. Treatment for pulmonary hypertension given according to the groups of pulmonary hypertension they belong. Pulmonary arterial hypertension patients are treated according to the functional class they presented either with calcium channel blockers, endothelial receptor antagonist ,prostanoids.

Clinical assessment of pulmonary hypertension using WHO functional class showed improved after treatment with groups 1,2 and 3. Group 4 and 5 didn’t show improvement and worsened as surgery being the treatment option in group 4 and group 5 has multifactorial mechanisms and aetiology and poorer prognosis.

Severity of pulmonary hypertension with treatment:

51% of patients who were initially diagnosed as moderate PT, after treatment reduced to 37 %. 32% of patients with severe pulmonary hypertension reduced to 26% following treatment. The response to treatment was good with groups 2 and 3 compared to other groups.

Response in patients with moderate hypertension was found to be better than severe groups may be due to onset of irreversible changes and progression of disease. Patients needs to be diagnosed early and treatment initiated early for better response.

The presence of right atrial and ventricular dilatation continues to be present after treatment. May be functional improvement occurs earlier than the anatomical changes takes place. Need for a longer treatment and follow up studies for the anatomical improvement to take place.

CONCLUSION

CONCLUSION

Pulmonary hypertension is the ultimate end result of alteration in pulmonary vasculature initiated and propagated by diverse pathologic mechanisms. Platelets are closely associated in both initiation and progression of disease. Platelet activation is associated with all groups of pulmonary hypertension.

Platelet indices are found to be altered in all causes of pulmonary hypertension. Thrombocytopenia is found to be a independent predictor of poor prognosis and mortality among patients with pulmonary hypertension

Most of the cases of pulmonary hypertension are diagnosed only after development of moderate hypertension. It should be suspected whenever patients present with overlapping symptoms of cardiac and respiratory illness. Especially among patients having high risk factors for pulmonary hypertension like connective tissue diseases, periodic screening with echocardiogram is indicated.

Echocardiographic evidence massive of RA/RV dilataion, TAPSE< 16, pericardial effusion are associated with severe pulmonary hypertension and indicate a poorer prognosis.

The difference in prevalence of PH among sexes and Aetiology in Indian subcontinent is noted. May be due the increased incidence of COPD due to smoking and post infectious sequel of tuberculosis which is rising. Most of the COPD patients presents with mild to moderate pulmonary hypertension. Extensive studies in pulmonary hypertension are conducted mostly in western population, the difference in aetiology and ethnicity in Indian population calls for a registry for pulmonary hypertension in India.

Treatment should be initiated after classification of patients to appropriate groups, as the aetiology and treatment is different for each group. The treatment response after development of severe hypertension is reduced. Earlier detection and early initiation of appropriate treatment is indicated.

Following treatment, Functional improvement occurs earlier than the anatomical improvement which calls for a longer duration of treatment and follow up.

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ANNEXURES

ABBREVIATIONS

CO	:	cardiac output
mPAP	:	mean pulmonary artery pressure
BMPR2	:	bone morphogenic protein receptor 2
RHC	:	right heart catherisation
NIH	:	National institute of health
PAWP	:	pulmonary artery wedge pressure
PVR	:	pulmonary vascular resistance
TPR	:	Total pulmonary resistance
PAH	:	pulmonary aterial hypertension
TAPSE	:	tricuspid annular plance systolic excursion
CTEPH	:	chronic thrombo embolic pulmonary hypertension

PROFORMA

Assessment of Platelets in patient with pulmonary hypertension

Name: Age: Sex:

Patient ID: Contact number: Occupation:

- NAME:
- AGE:
- SEX:
- OP NUMBER:

- **PAST HISTORY** – HYPERTENSION: CAD: PVD:

  STROKE: RENAL DISEASE:

  PREGNANCY - YES: NO: N/A

- **CLINICAL EXAMINATION**:
- PALLOR:
- ICTERUS:

- CYANOSIS:
- CLUBBING:
- GENERALIZED LYMPAHADENOPATHY:
- PEDAL EDEMA:

- **SYSTEMIC EXAMINATION**: CVS:

RS:

CNS:

PA:

INVESTIGATIONS:

1. **Complete blood count and peripheral smear:**
2. **Bleding test**
3. **Clotting test**
4. **ECG:**

5. ECHOCARDIOGRAPHY FINDINGS:

a) Pulmonary artery pressure assessement:

TR jet velocity:

PSAP: 4x (TR jet velocity)

mPAP:

severity:

b) RV function assessment

RA dimension

RV dimension

RV function - TAPSE

c) LV function assessment

LVID (diastolic) (systolic) EF

d) valves

PE/Clot

Others

INFORMATION SHEET

- We are conducting a study on "**Assessment of platelets in patients with pulmonary hypertension"** among outpatients visiting Government General Hospital, Chennai and for that your sample may be valuable to us.

- The purpose of this study is to study the platelet function and morphology in patients with pulmonary hypertension and its correlation with severity of pulmonary hypetension. And also the effect of treatment of pulmonary hypertension on platelets

- We are selecting certain cases and if your specimen is found eligible, we may be using your 4ml of blood sample to be collected in EDTA for platelet count and mean platelet volume . We also need to take an ECG and perform a 2D echocardiography and colour Doppler to assess the pulmonary hypertension.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date:

ஆராய்ச்சி தகவல் தாள்

நுரையீரலில் உள்ள உயர் இரத்த அழுத்ததினால் பாதிக்கப்படும் நோயாளிகளின் தட்டனுக்களில் ஏற்படும் மாற்றம் பற்றிய ஆராய்ச்சி

இந்த ஆராய்ச்சியில் உங்களிடம் இருந்து 4.மி.லி இரத்தம் எடுத்து இரத்த அணுக்களின் பரிசோதனை, இருதய சுருள் படம், மார்பக கதிர்வீச்சு, இருதய எதிரொலிப்பு செய்யப்படும். இரண்டு மாதம் மருத்துவ சிகிச்சைக்கு பின்பு மீண்டும் அனைத்து பரிசோதனைகளும் செய்யப்படும். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள்:

இடம்:

PATIENT CONSENT FORM

Study Title	:	**Assessment of platelets in patients with pulmonary hypertension"**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ❑

Signature/thumb impression

Signature of Investigator

Patient's Name and Address:

Study Investigator's Name:

Dr. V.GOVARDHINI

ஆராய்ச்சி ஒப்புதல் கடிதம்

<u>ஆராய்ச்சி தலைப்பு:</u> நுரையீரலில் உள்ள உயர் இரத்த அழுத்ததினால் பாதிக்கப்படும் நோயாளிகளின் தட்டனுக்களில் ஏற்படும் மாற்றம் பற்றிய ஆராய்ச்சி

இந்த ஆராய்ச்சியில் உங்களிடம் இருந்து 4.மி.லி இரத்தம் எடுத்து இரத்த அணுக்களின் பரிசோதனை, இருதய சுருள் படம், மார்பக கதிர்வீச்சு, இருதய எதிரொலிப்பு செய்யப்படும். இரண்டு மாதம் மருத்துவ சிகிச்சைக்கு பின்பு மீண்டும் அனைத்து பரிசோதனைகளும் செய்யப்படும்.

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடன் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள்:

இடம்:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.V.Govardhini
Postgradaute M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.V.Govardhini,

The Institutional Ethics Committee has considered your request and approved your study titled **"Assessment of Platelets in patients with Pulmonary Hypertension" No.14052015.**

The following members of Ethics Committee were present in the meeting held on 12.05.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
8. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

15/6/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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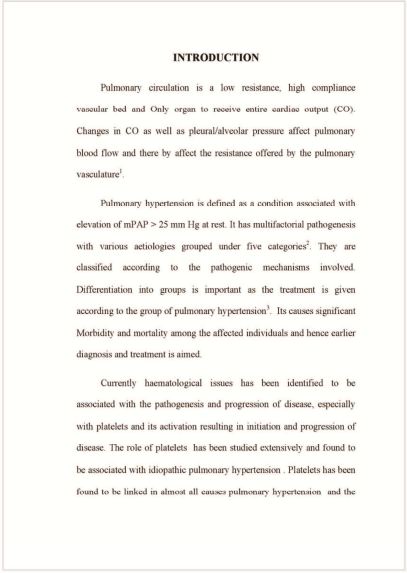
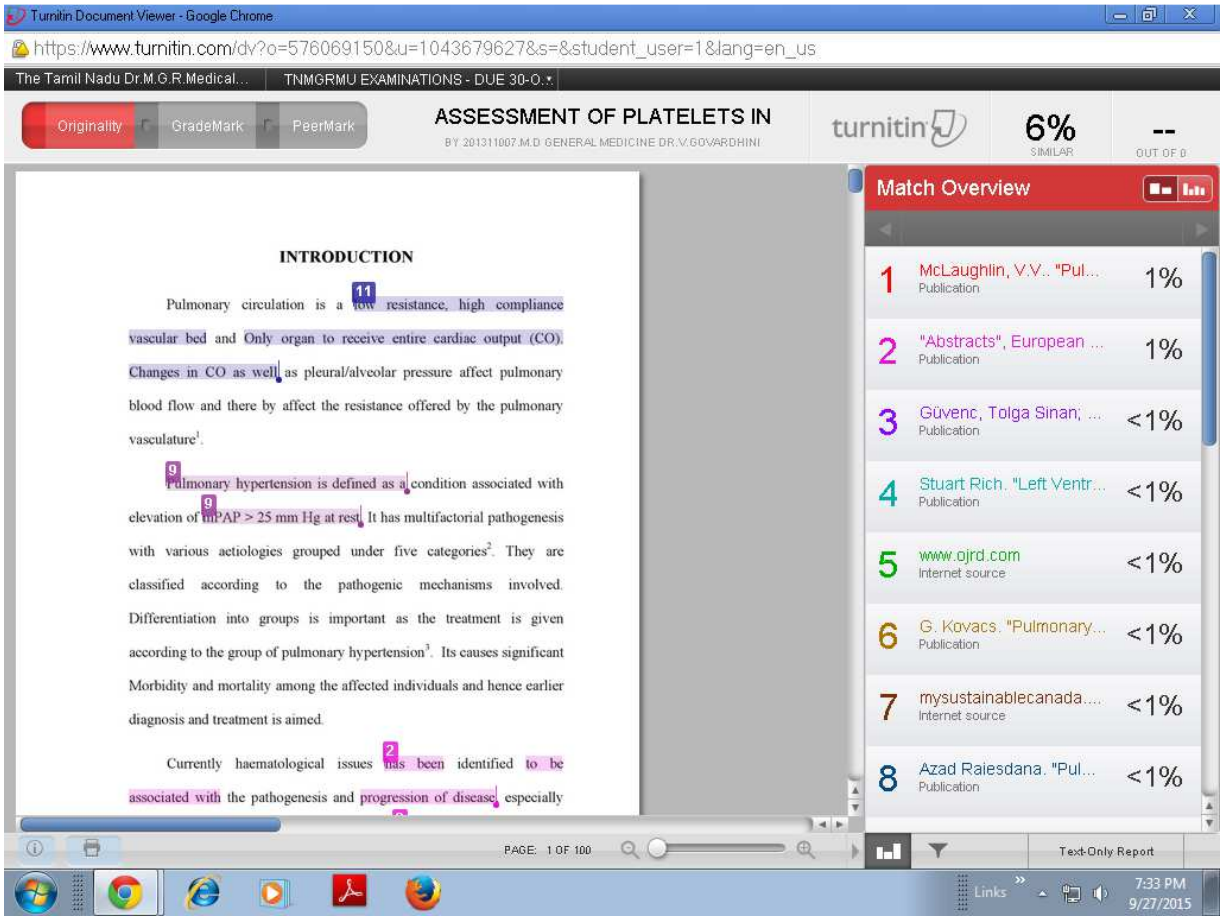


INTRODUCTION

Pulmonary circulation is a low resistance, high compliance vascular bed and Only organ to receive entire cardiac output (CO). Changes in CO as well as pleural/alveolar pressure affect pulmonary blood flow and there by affect the resistance offered by the pulmonary vasculature[1].

Pulmonary hypertension is defined as a condition associated with elevation of mPAP > 25 mm Hg at rest. It has multifactorial pathogenesis with various aetiologies grouped under five categories[2]. They are classified according to the pathogenic mechanisms involved. Differentiation into groups is important as the treatment is given according to the group of pulmonary hypertension[3]. Its causes significant Morbidity and mortality among the affected individuals and hence earlier diagnosis and treatment is aimed.

Currently haematological issues has been identified to be associated with the pathogenesis and progression of disease, especially with platelets and its activation resulting in initiation and progression of disease. The role of platelets has been studied extensively and found to be associated with idiopathic pulmonary hypertension . Platelets has been found to be linked in almost all causes pulmonary hypertension and the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INTRODUCTION
Pulmonary circulation is a low resistance, high compliance vascular bed and Only organ to receive entire cardiac output (CO). Changes in CO as well as pleural/alveolar pressure affect pulmonary blood flow and there by affect the resistance offered by the pulmonary vasculature[1].
Pulmonary hypertension is defined as a condition associated with elevation of mPAP > 25 mm Hg at rest. It has multifactorial pathogenesis with various aetiologies grouped under five categories[2]. They are classified according to the pathogenic mechanisms involved. Differentiation into groups is important as the treatment is given according to the group of pulmonary hypertension[3]. Its causes significant Morbidity and mortality among the affected individuals and hence earlier diagnosis and treatment is aimed.
Currently haematological issues has been identified to be associated with the pathogenesis and progression of disease especially
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							INITIAL ASSESSMENT																						REVIEW AFTER 2 MTHS TREATMENT																			
							HAEMOGRAM							ECHOCARDIOGRAM																																		
														PASP	mPAP	RV FUNCTION		LV FUNCTION																													
S.NO	AGE	SEX	IP NO	ETIOLOGY	CLASSIFICATION OF PHT	FUNCTIONAL CLASS	TTCx10^3	MPV fL	PDW	P-LCR	P.SMEAR	BLEEDING TIME	CLOTTING TIME	4TRV²+RA	0.61xPSAP+2	RA,RV DIMENSION	TAPSE	SYSTOLIC FN	DIASTOLIC FN	EF %	VALVES	PERICARDIAL EFFUSION/CLOT	SEVERITY	FUNCTIONAL CLASS	TTCx10^3	MPV fL	PDW	P-LCR	4TRV²+RA	0.61xPSAP+2	RA,RV DIMENSION	TAPSE	SYSTOLIC FN	DIASTOLIC FN	EF %	VALVES	PERICARDIAL EFFUSION/CLOT	SEVERITY
1	24	F	36901	BRONCHIECTASIS/C	3	3	1.03	11	19	38	LARGE PLATELETS	4 0"	3 30"	67.2	43	DILATED	12	N	N	65	NORMA	NO	MODERATE	2	2	11	18	35	64	41	DILATED	14	N	-	65	NORMA	NO	MODERATE
2	52	F	39427	OLD PT/COPD	3	3	1.67	11	18	35	NORMAL	3 30"	4 0"	70.5	45	DILATED	14	N	N	63	NORMA	NO	MODERATE	2	2	10.3	20	28	67.2	43	DILATED	16	N	N	65	NORMA	NO	MODERATE
3	50	F	39560	PAH-IDOPATHIC	1	4	1.5	12	19	36	LARGE PLATELETS	4 30"	4 30"	73.9	47.1	DILATED	11	N	N	60	TR MILI	NO	MODERATE	3	2	11	19	35	70.5	45	DILATED	11	N	N	60	TR MIL	NO	MODERATE
4	65	F	40070	PAH-CTD	1	4	1.35	11	19	30	LARGE PLATELETS	4 0"	4 0"	88.3	55.8	DILATED	12	N	N	55	TR MODRATE	NO	SEVERE	3	1.5	11.3	19	29	88.36	55.8	DILATED	12	N	N	58	TR MIL	NO	SEVERE
5	45	M	40089	OLD PT/COPD	3	2	2.02	10	18	30	NORMAL	3 30"	4 30"	46.2	30.2	NORMAL	16	N	N	65	NORMA	NO	MILD	1	2.4	10.3	18	32	43.56	28.5	NORMAL	16	N	N	65	NORMA	NO	MILD
6	58	M	40156	OLD PT/COPD	3	4	0.94	11	20	38	THROMBOCYTOPENIA	5 0"	4 0"	88.3	55.8	DILATED	16	N	N	60	TR MILI	MILD F	SEVERE	3	1.7	11.5	19	35	88.36	55.8	DILATED	16	N	N	60	TR MI	NO	SEVERE
7	48	F	41835	VALVULAR HD	2	4	1.56	10	14	30	NORMAL	4 0"	5 30"	92.2	58.2	DILATED	17	N	N	65	MS/MR	NO	SEVERE	3	1.7	9.8	14	28	88.4	55.8	DILATED	17	N	N	65	MS MO	NO	SEVERE
8	52	M	41850	LV SYS DYFN	2	4	2.46	9.9	12	20	NORMAL	3 30"	4 30"	88.4	55.8	DILATED	16	+	N	30	MR MIL	NO	SEVERE	3	2.5	9.5	12	19	81	51.4	DILATED	16	+	N	35	MR MIL	NO	MODERATE
9	46	M	42050	OLD PT/COPD	3	2	2.58	9	11	16	NORMAL	3 0"	4 30"	46.2	30.2	NORMAL	17	N	N	65	NORMA	NO	MILD	2	2.7	9	12	15	46.24	30.2	NORMAL	17	N	N	65	NORMA	NO	MILD
10	65	M	42506	OLD PT/COPD	3	3	1.98	11	13	28	NORMAL	3 0'	4 0"	81	51.4	DILATED	18	N	N	50	NORMA	NO	MODERATE	LOST REVIEW														
11	37	M	42586	CTEPH	4	4	2.04	11	15	25	NORMAL	3 30"	5 30"	92.1	58.2	DILATED	14	N	N	68	TR MILI	NO	SEVERE	4	2.5	10.5	16	28	88.36	55.8	DILATED	15	N	N	65	TR MIL	NO	SEVERE
12	35	F	42670	VALVULAR HD	2	2	2.5	9.5	16	26	NORMAL	4 0"	3 00"	40.9	27	NOMAL	17	N	N	60	MS MOI	NO	MILD	2	3.1	9.2	16	26	40.9	27	NORMAL	17	N	N	60	MS MO	NO	MILD
13	40	M	32879	OLD PT/COPD	3	2	2.4	8.6	15	23	NORMAL	3 0"	3 30"	43.5	28.5	NORMAL	16	N	N	65	NORMA	NO	MILD	2	2.7	8.6	15	24	40.9	27	NORMAL	17	N	N	65	NORMA	NO	MILD
14	50	F	33056	ILD	3	3	1.46	11	16	28	LARGE PLATELETS	4 0"	4 0"	84.6	53.6	DILATED	15	N	N	60	NORMA	NO	MODERATE	3	1.6	10	16	28	88.36	55.8	DILATED	15	N	N	60	TR MIL	NO	SEVERE
15	46	M	33067	OLD PT/COPD	3	3	2.06	10	18	25	NORMAL	3 30"	4 30"	64	41	DILATED	17	N	N	63	NORMA	NO	MODERATE	2	2.4	10.4	18	25	54.76	35.4	DILATED	17	N	N	63	NORMA	NO	MILD
16	24	F	33128	VALVULAR HD	2	4	1.6	11	17	28	LARGE PLATELETS	4 0"	4 0"	88.4	55.8	DILATED	15	N	N	60	SEVERE	NO	SEVERE	3	1.8	10.5	17	28	81	51.41	DILATED	15	N	N	60	MS SEV	NO	MODERATE
17	68	M	33145	LV DAS DYFN	2	3	2.05	11	18	26	NORMAL	3 0"	4 30"	64	41.04	DILATED	17	N	+	55	MODER	NO	MODERATE	2	2.4	10.6	18	27	54.76	35.4	DILATED	17	N	+	55	MILD M	NO	MILD
18	55	F	33209	OSA/ MORBID OBES	3	4	1.39	11	18	29	LARGE PLATELETS	3 30"	4 0"	92.2	58.21	DILATED	15	N	N	58	MILD TI	MILD F	SEVERE	4	1.6	11	18	27	88.36	55.8	DILATED	15	N	N	55	MILD TI	NO	SEVERE
19	35	F	33245	ILD	3	2	2.56	11	15	26	NORMAL	4 0"	5 30"	70.6	45	DILATED	16	N	N	60	NORMA	NO	MODERATE	3	2.6	10.5	17	28	70.56	45	DILATED	16	N	N	60	MILD TI	NO	MODERATE
20	56	M	33450	BRONCHIECTASIS/C	3	2	2.48	10	16	25	NORMAL	4 0"	4 30"	49	31.9	NORMAL	17	N	N	60	normal	NO	MILD	2	2.7	9.9	16	26	46.2	30.2	NORMAL	17	N	N	63	NORMA	NO	MILD
21	45	M	33560	VALVULAR HD	2	3	2.04	10	15	26	NORMAL	3 0"	4 0"	70.5	45	DILATED	16	N	N	58	MS/MR	NO	MODERATE	3	2.5	10.2	15	24	64	41	DILATED	16	N	N	60	MS/MR	NO	MODERATE
22	60	F	33659	OLD PT/COPD	3	4	1.95	11	18	28	PLATELE	2 0"	5 30"	96	60.5	DILATED	16	N	N	63	MILD TI	MILD F	SEVERE	LOST REVIEW PATIENT EXPIRED														
23	35	F	33680	VSD	2	3	2.05	9.4	15	24	NORMAL	3 '0	4 0"	67.2	43	DILATED	17	N	N	58	MILD M	NO	MODERATE	2	2.5	9.4	16	25	64	41.04	DILATED	17	N	N	58	MILD M	NO	MODERATE
24	70	M	33760	OLD PT/COPD	3	3	1.97	11	18	26	NORMAL	4 30"	4 30"	64	41.04	DILATED	17	N	N	55	normal	NO	MODERATE	2	2.5	10.5	18	27	60.84	39.11	DILATED	18	N	N	58	NORMA	NO	MILD
25	26	F	33798	VALVULAR HD	2	2	2.67	9.8	15	21	NORMAL	3 30"	4 0"	43.6	28.5	NORMAL	18	N	N	63	MODER	NO	MILD	2	2.6	9.4	16	20	40.96	27	NORMAL	18	N	N	63	MODER	NO	MILD
26	38	M	33887	VALVULAR HD	2	3	2.85	9.7	16	22	NORMAL	3 0"	4 30"	46.2	30.2	NORMAL	18	N	N	65	MODER	NO	MILD	3	2.9	9.5	16	21	43.56	28.5	NORMAL	18	N	N	65	MODER	NO	MILD
27	55	F	33890	ILD	3	4	1.56	11	19	28	LARGE PL	2 0"	4 0"	92.2	58.21	DILATED	14	N	N	55	MILD TI	NO	SEVERE	4	1.7	11	19	27	96.04	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE
28	66	M	43896	LV SYS DYFN	2	4	2.08	11	18	24	LARGE PL	3 0"	5 30"	67.2	43	DILATED	17	+	N	28	MODEA	CLOT+	MODERATE	3	2.2	10.5	18	25	57.76	37.23	DILATED	17	+	N	35	MILD M	NO	MILD
29	32	F	44675	VSD	2	3	2.2	11	18	23	NORMAL	3 30"	3 30"	70.6	45	DILATED	18	N	N	58	VSDMIL	NO	MODERATE	2	2.3	10.4	18	23	64	41.04	DILATED	18	N	N	58	VSDMIL	NO	MODERATE
30	56	F	44765	OSA/ MORBID OBES	3	4	0.98	12	19	32	LARGE PL	2 30"	4 0"	96	60.5	DILATED	14	N	N	55	MODER	MILD F	SEVERE	LOST REVIEW PATIENT EXPIRED														
31	45	M	44776	CTEPH	4	3	2.45	11	18	30	LARGE PL	3 0"	4 30"	67.2	43	DILATED	16	N	N	60	MILD M	NO	MODERATE	2	2.5	10.5	18	29	67.24	43	DILATED	16	N	N	60	MILD TI	NO	MODERATE

32	40	F	44786	PAH-CTD	1	4	1.56	11	19	32	LARGE PL	2 30"	4 0"	92.2	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE	3	1.7	11.3	18	30	92.16	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE
33	58	M	44877	OLD PT/COPD	3	3	2.13	11	17	30	LARGE PL	3 0"	4 30"	64	41.04	DILATED	16	N	N	60	MILD T	NO	MODERATE	2	2.3	10.7	17	28	57.7	37.2	DILATED	15	N	N	60	NORMA	NO	MILD
34	34	F	43986	VALVULAR HD	2	3	1.96	10	15	25	LARGE PL	4 0"	4 0"	64	41	NORMAL	17	N	N	63	MS MO	NO	MODERATE	2	2.1	10.2	15	25	60.8	39.1	NORMAL	17	N	N	53	MS MO	NO	MILD
35	45	M	43994	LV DAS DYFN	2	3	1.86	10	18	28	NORMAL	3 30"	5 30"	70.6	45	DILATED	17	N	+	55	MR MIL	NO	MODERATE	2	2	10.3	16	25	64	41.04	DILATED	17	N	+	55	MILD M	NO	MODERATE
36	45	F	44009	PAH-IDOPATHIC	1	4	1.45	11	19	30	LARGE PL	4 0"	4 30"	92.1	58.2	DILATED	13	N	N	65	MILD T	NO	SEVERE	3	1.5	11	19	28	88.36	55.8	DILATED	15	N	N	65	MILD T	NO	SEVERE
37	60	F	44150	OSA/ MORBID OBES	3	4	1.38	11	17	27	LARGE PL	4 30"	3 30"	96	60.6	DILATED	14	N	N	58	MILD T	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE
38	58	M	44258	OLD PT/COPD	3	4	2.06	11	18	28	LARGE PL	4 0"	3 30"	88.4	55.8	DILATED	15	N	N	55	MILD T	NO	SEVERE	3	2.2	10.5	17	27	81	51.4	DILATED	17	N	N	60	MILD T	NO	MODERATE
39	62	M	44568	LV SYS DYFN	2	2	2.47	9.9	15	27	NORMAL	4 30"	4 0"	46.2	30.2	DILATED	15	+	N	40	MILD M	NO	MILD	2	2.6	9.9	15	25	43.5	28.5	DILATED	18	+	N	45	NORMA	NO	MILD
40	48	M	44598	BRONCHIECTASIS/C	3	3	1.89	11	15	26	NORMAL	4 0"	4 30"	70.6	45	DILATED	16	N	N	63	NORMA	NO	MODERATE	2	2.1	10.4	16	26	60	39.1	DILATED	16	N	N	65	NORMA	NO	MILD
41	29	F	44678	PAH-HIV	1	4	1.08	11	19	30	LARGE PL	5 30"	4 0"	92.2	58.21	DILATED	14	N	N	60	MILD T	NO	SEVERE	3	1.1	10.7	19	29	88.36	55.8	DILATED	14	N	N	60	MILD T	NO	SEVERE
42	39	M	44769	VALVULAR HD	2	3	2.45	11	17	27	NORMAL	40"	4 30"	81	51.41	DILATED	15	N	N	65	MS MO	NO	MODERATE	2	2.6	10.5	18	27	64	41	DILATED	16	N	N	65	MS MO	NO	MODERATE
43	50	M	44890	OLD PT/COPD	3	2	1.98	11	18	25	LARGE PL	4 30"	4 0"	43.6	28.5	DILATED	17	N	N	65	NORMA	NO	MILD	2	2	10.5	16	25	40.96	27	NORMAL	17	N	N	65	NORMA	NO	MILD
44	40	M	44950	OLD PT/COPD	3	2	2.15	11	17	27	NORMAL	3 30"	5 30"	41	27	NORMAL	18	N	N	60	NORMA	NO	MILD								LOST REVIEW							
45	26	M	46796	ASD	2	3	2.34	9.6	17	26	NORMAL	3 0"	4 0"	67.2	43	DILATED	18	N	N	58	VSDMIL	NO	MODERATE	2	2.4	9.5	17	26	64	41.04	DILATED	18	N	N	60	VSDMIL	NO	MODERATE
46	42	F	46901	BRONCHIECTASIS/C	3	3	2.05	11	18	27	LARGE PL	3 0"	4 30"	70.5	45	DILATED	17	N	N	60	NORMA	NO	MODERATE	2	2.1	10.5	18	27	60.8	39.1	DILATED	17	N	N	60	NORMA	NO	MILD
47	52	F	49427	OLD PT/COPD	3	2	2.13	11	17	30	LARGE PL	3 0"	3 0'	64	41.04	DILATED	16	N	N	60	MILD T	NO	MODERATE	2	2.3	10.7	17	28	57.7	37.2	DILATED	15	N	N	60	NORMA	NO	MILD
48	45	F	49560	PAH-IDOPATHIC	1	3	1.56	11	19	32	LARGE PL	2 30"	4 30"	92.2	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE	3	1.7	11.3	18	30	92.16	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE
49	50	F	50070	PAH-CTD	1	3	2.56	11	15	26	NORMAL	4 0"	3 30"	70.6	45	DILATED	16	N	N	60	NORMA	NO	MODERATE	3	2.6	10.5	17	28	70.56	45	DILATED	16	N	N	60	MILD T	NO	MODERATE
50	45	M	51089	OLD PT/COPD	3	2	1.97	11	18	26	NORMAL	4 30"	4 00"	64	41.04	DILATED	17	N	N	55	normal	NO	MODERATE	2	2.5	10.5	18	27	60.84	39.11	DILATED	18	N	N	58	NORMA	NO	MILD
51	58	M	53156	OLD PT/COPD	3	3	1.98	11	13	28	NORMAL	3 0'	4 0"	81	51.4	DILATED	18	N	N	50	NORMA	NO	MODERATE		LOST REVIEW													
52	58	M	54994	LV SYS DYFN	2	3	2.46	9.9	15	27	NORMAL	4 30"	4 30"	46.2	30.2	DILATED	15	+	N	40	MILD M	NO	MILD	2	2.6	9.9	15	25	43.5	28.5	DILATED	18	+	N	45	NORMA	NO	MILD
53	48	F	54009	PAH-IDOPATHIC	1	4	1.5	12	19	36	large platelets	4 30"	3 0'	73.9	47.1	dilated	11	N	N	60	TR mild	NO	moderate	3	2	11	19	35	70.5	45	dilated	11	N	N	60	TR mild	NO	moderate
54	56	F	54150	OSA/ MORBID OBES	3	4	1.38	11	17	27	LARGE PL	4 30"	4 30"	96	60.6	DILATED	14	N	N	58	MILD T	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE
55	75	M	54268	OLD PT/COPD	3	4	2.06	11	18	28	LARGE PL	4 0"	3 30"	88.4	55.8	DILATED	15	N	N	55	MILD T	NO	SEVERE	3	2.2	10.5	17	27	81	51.4	DILATED	17	N	N	60	MILD T	NO	MODERATE
56	62	M	54578	LV SYS DYFN	2	2	1.86	10	18	28	NORMAL	3 30"	3 '0	70.6	45	DILATED	17	+	N	58	MR MIL	NO	MODERATE	2	2	10.3	16	25	64	41.04	DILATED	17	+	N	33	MILD M	NO	MODERATE
57	47	M	54598	OLD PT/COPD	3	2	2.13	11	17	29	LARGE PL	3 30"	4 30"	64	41.04	DILATED	16	N	N	60	MILD T	NO	MODERATE	2	2.3	10.7	17	28	57.7	37.2	DILATED	15	N	N	60	NORMA	NO	MILD
58	36	F	56798	VALVULAR HD	2	2	2.15	11	17	27	NORMAL	3 30"	4 30"	41	27	DILATED	18	N	N	60	MODER	NO	MILD								LOST REVIEW							
59	24	M	57887	VALVULAR HD	2	3	1.96	10	15	25	LARGE PL	4 0"	4 0"	64	41	NORMAL	17	N	N	63	MS MO	NO	MODERATE	2	2.1	10.2	15	25	60.8	39.1	NORMAL	17	N	N	53	MS MO	NO	MILD
60	52	F	58890	ILD	3	4	1.56	11	19	28	LARGE PL	2 0"	4 30"	92.2	58.21	DILATED	14	N	N	55	MILD T	MILD P	SEVERE	4	1.7	11	19	27	96.04	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE
61	68	M	63896	LV SYS DYFN	2	4	2.46	9.9	12	20	NORMAL	3 30"	4 0"	88.4	55.8	DILATED	16	+	N	28	MR MIL	NO	SEVERE	3	2.5	9.5	12	19	81	51.4	DILATED	16	+	N	35	MR MIL	NO	MODERATE
62	32	M	64675	VSD	2	3	2.05	9.4	15	24	NORMAL	3 '0	5 30"	67.2	43	DILATED	17	N	N	58	VSD MI	NO	MODERATE	2	2.5	9.4	16	25	64	41.04	DILATED	17	N	N	58	VSD MI	NO	MODERATE
63	46	F	64765	OSA/ MORBID OBES	3	4	1.38	11	17	27	LARGE PL	4 30"	5 00"	96	60.6	DILATED	14	N	N	58	MILD T	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE
64	45	M	64776	CTEPH	4	4	1.38	11	17	27	LARGE PL	4 30"	4 30"	96	60.6	DILATED	14	N	N	58	MILD T	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE
65	40	F	64786	PAH-CTD	1	3	2.56	11	15	26	NORMAL	4 0"	3 30"	70.6	45	DILATED	16	N	N	60	NORMA	NO	MODERATE	3	2.6	10.5	17	28	70.56	45	DILATED	16	N	N	60	MILD T	NO	MODERATE
66	68	F	64568	LV SYS DYFN	2	2	2.36	9.9	15	27	NORMAL	4 30"	4 0"	46.2	30.2	DILATED	15	+	N	28	MILD M	NO	MILD	2	2.6	9.9	15	25	43.5	28.5	DILATED	18	+	N	45	NORMA	NO	MILD
67	48	F	64598	OLD PT/COPD	3	3	1.89	11	15	26	NORMAL	4 0"	4 30"	70.6	45	DILATED	16	N	N	63	NORMA	NO	MODERATE	2	2.1	10.4	16	26	60	39.1	DILATED	16	N	N	65	NORMA	NO	MILD
68	49	M	64678	PAH-CTD	1	4	1.08	11	19	30	LARGE PL	5 30"	4 0"	92.2	58.21	DILATED	14	N	N	60	MILD T	NO	SEVERE	3	1.1	10.7	19	29	88.36	55.8	DILATED	14	N	N	60	MILD T	NO	SEVERE
69	49	M	64769	VALVULAR HD	2	3	2.45	11	17	27	NORMAL	40"	4 30"	81	51.41	DILATED	15	N	N	65	MS MO	NO	MODERATE	2	2.6	10.5	18	27	64	41	DILATED	16	N	N	65	MS MO	NO	MODERATE
70	50	M	64890	OLD PT/COPD	3	2	1.98	11	18	25	LARGE PL	4 30"	4 0"	43.6	28.5	DILATED	17	N	N	65	NORMA	NO	MILD	2	2	10.5	16	25	40.96	27	NORMAL	17	N	N	65	NORMA	NO	MILD
71	45	F	64950	PAH-IDOPATHIC	3	2	2.15	11	17	27	NORMAL	3 30"	5 30"	41	27	NORMAL	18	N	N	60	NORMA	NO	MILD								LOST REVIEW							
72	46	M	66796	ASD	2	3	2.34	9.6	17	26	NORMAL	3 0"	4 30"	67.2	43	DILATED	18	N	N	58	VSDMIL	NO	MODERATE	2	2.4	9.5	17	26	64	41.04	DILATED	18	N	N	60	VSDMIL	NO	MODERATE
73	48	M	67009	OTHERS-SARCOIDO	1	4	1.5	12	19	36	large platelets	4 30"	4 0"	73.9	47.1	dilated	11	N	N	60	TR mild	NO	moderate	3	2	11	19	35	70.5	45	dilated	11	N	N	60	TR mild	NO	moderate
74	56	F	67150	OSA/ MORBID OBES	3	4	1.38	11	17	27	LARGE PL	4 30"	3 30"	96	60.6	DILATED	14	N	N	58	MILD T	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE
75	75	M	68268	BRONCHIECTASIS/C	3	4	2.06	11	18	28	LARGE PL	4 0"	4 30"	88.4	55.8	DILATED	15	N	N	55	MILD T	NO	SEVERE	3	2.2	10.5	17	27	81	51.4	DILATED	17	N	N	60	MILD T	NO	MODERATE
76	52	M	68578	LV DAS DYFN	2	2	2.26	10	18	27	NORMAL	3 30"	4 0"	64	41.04	DILATED	17	N	+	28	MR MIL	NO	MODERATE	2	2	10.3	16	25	64	41.04	DILATED	17	N	+	55	MILD M	NO	MODERATE
77	47	M	68598	OLD PT/COPD	3	2	2.13	11	17	29	LARGE PL	3 30"	3 30"	64	41.04	DILATED	16	N	N	60	MILD T	NO	MODERATE	2	2.3	10.7	17	28	57.7	37.2	DILATED	15	N	N	60	NORMA	NO	MILD

78	36	F	68798	OLD PT/COPD	3	3	2.15	11	17	27	LARGE PL	3 30"	2 30"	41	27	DILATED	18	N	N	60	NORMA	NO	MILD	LOST REVIEW															
79	70	M	69659	OLD PT/COPD	3	4	1.95	11	18	28	LARGE PLATELE	2 0"	4 0"	96	60.5	DILATED	16	N	N	63	MILD TI	NO	SEVERE	LOST REVIEW PATIENT EXPIRED															
80	25	F	69680	VSD	2	3	2.05	9.4	15	24	NORMAL	3 '0	3 '0	67.2	43	DILATED	17	N	N	58	MILD M	NO	MODERATE	2	2.5	9.4	16	25	64	41.04	DILATED	17	N	N	58	MILD M	NO	MODERATE	
81	70	M	69760	OLD PT/COPD	3	3	1.97	11	18	26	NORMAL	4 30"	4 30"	64	41.04	DILATED	17	N	N	55	normal	NO	MODERATE	2	2.5	10.5	18	27	60.84	39.11	DILATED	18	N	N	58	NORMA	NO	MILD	
82	50	F	69762	LV DAS DYFN	2	4	2.02	11	16	25	NORMAL	3 30"	3 00"	64	41	RESTRICTED	16	N	+	55	NORMA	PE	MODERATE	3	2.1	10.5	16	25	57.7	37.2	RESTRICTED	16	N	+	55	NORMA	PE+	MILD	
83	36	M	69780	CHEST DEFORMITIE	3	3	1.38	11	17	27	LARGE PL	4 30"	4 30"	96	60.6	DILATED	14	N	N	58	MILD TI	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE	
84	45	M	69880	LV DAS DYFN	2	4	1.45	11	16	27	LARGE PL	3 0"	3 30"	64	41	RESTRICTED	17	N	+	55	NORMA	PE	MODERATE	3	1.8	10.7	15	27	60.84	39.11	RESTRICTED	17	N	+	55	NORMA	PE+	MILD	
85	42	F	69901	CHEST DEFORMITIE	3	3	2.05	11	18	27	LARGE PL	3 0"	4 0"	70.5	45	DILATED	17	N	N	60	NORMA	NO	MODERATE	3	2.1	10.5	18	27	70.6	45	DILATED	17	N	N	60	NORMA	NO	MODERATE	
86	52	F	69427	OLD PT/COPD	3	2	2.13	11	17	30	LARGE PL	3 0"	3 '0	64	41.04	DILATED	16	N	N	60	MILD TI	NO	MODERATE	2	2.3	10.7	17	28	57.7	37.2	DILATED	15	N	N	60	NORMA	NO	MILD	
87	45	F	69560	PAH-CTD	1	3	1.56	11	19	32	LARGE PL	2 30"	4 30"	92.2	58.21	DILATED	14	N	N	55	MODERATE MR		SEVERE	3	1.7	11.3	18	30	92.16	58.21	DILATED	14	N	N	55	MODER	NO	SEVERE	
88	50	F	70070	PAH-HIV	1	3	2.56	12	18	30	NORMAL	4 0"	3 30"	70.6	45	DILATED	16	N	N	60	NORMA	NO	MODERATE	3	2.6	10.5	17	28	70.56	45	DILATED	16	N	N	60	MILD T	NO	MODERATE	
89	36	M	72675	VSD	2	3	2.05	9.4	15	24	NORMAL	3 '0	4 30"	67.2	43	DILATED	17	N	N	58	VSD MILD MR		MODERATE	2	2.5	9.4	16	25	64	41.04	DILATED	17	N	N	58	VSD MI	NO	MODERATE	
90	36	M	72765	OSA/ MORBID OBES	3	4	1.38	11	17	27	LARGE PL	4 30"	4 00"	96	60.6	DILATED	14	N	N	58	MILD TI	NO	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE	
91	32	M	73675	PDA	2	3	2.05	9.4	15	24	NORMAL	3 0"	4 30"	67.2	43	DILATED	17	N	N	58	NORMA	NO	MODERATE	2	2.5	9.4	16	25	64	41.04	DILATED	17	N	N	58	NORMA	NO	MODERATE	
92	46	F	73765	OSA/ MORBID OBES	3	4	1.38	11	17	30	LARGE PL	4 30"	5 00"	96	60.6	DILATED	14	N	N	58	MILD TI	PE	SEVERE	3	1.5	10.8	18	27	92.16	58.21	DILATED	15	N	N	58	MILD T	NO	SEVERE	
93	45	M	73776	CTEPH	4	4	1.58	11	18	29	LARGE PL	4 30"	5 30"	88.3	55.8	DILATED	15	N	N	55	MILD TI	NO	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	55	MILD T	NO	SEVERE	
94	24	F	73786	OTHERS-MPD	1	3	2.56	11	15	26	NORMAL	4 0"	4 00"	70.6	45	DILATED	16	N	N	60	NORMA	NO	MODERATE	3	2.6	10.5	17	28	70.56	45	DILATED	16	N	N	60	MILD T	NO	MODERATE	
95	46	M	74150	OSA/ MORBID OBES	3	4	1.38	11	17	27	LARGE PL	4 30"	4 0"	96	60.6	DILATED	14	N	N	58	MILD TI	MILD P	SEVERE	3	1.5	10.6	18	27	88.36	55.8	DILATED	15	N	N	58	MILD T	NO	SEVERE	
96	35	M	74268	OLD PT/COPD	3	4	1.89	11	18	28	LARGE PL	4 0"	3 30"	88.4	55.8	DILATED	15	N	N	55	MILD TI	NO	SEVERE	3	2.2	10.5	17	27	81	51.4	DILATED	17	N	N	60	MILD T	NO	MODERATE	
97	62	M	74578	LV SYS DYFN	2	2	1.96	11	18	28	NORMAL	3 30"	4 30"	70.6	45	DILATED	17	+	N	28	MR MIL	CLOT+	MODERATE	LOST REVIEW PT EXPIRED															
98	40	F	74786	ILD	3	3	2.56	11	15	30	NORMAL	4 0"	4 0"	70.6	45	DILATED	16	N	N	60	MILD TI	NO	MODERATE	3	2.6	10.5	17	28	70.56	45	DILATED	16	N	N	60	MILD T	NO	MODERATE	
99	58	F	74568	LV SYS DYFN	2	2	2.46	9.9	15	27	NORMAL	4 30"	3 30"	46.2	30.2	DILATED	15	+	N	28	MILD M	CLOT+	MILD	2	2.6	9.9	15	25	43.5	28.5	DILATED	18	+	N	45	NORMA	NO	MILD	
100	56	M	74598	CHEST DEFORMITIE	3	3	1.89	11	18	29	LARGE PL	4 0"	4 0"	70.6	45	DILATED	16	N	N	63	DILATE	NO	MODERATE	2	2.1	10.4	16	26	60	39.1	DILATED	16	N	N	65	NORMA	NO	MILD	
101	58	M	75156	OLD PT/COPD	3	3	1.98	11	13	28	NORMAL	3 0'	4 0"	81	51.4	DILATED	18	N	N	50	NORMA	NO	MODERATE		LOST REVIEW														
102	60	F	75994	LV SYS DYFN	2	3	2.25	9.9	15	27	NORMAL	4 30"	4 30"	46.2	30.2	DILATED	15	+	N	28	MILD M	NO	MILD	2	2.6	9.9	15	25	43.5	28.5	DILATED	18	+	N	45	NORMA	NO	MILD	
103	48	M	75009	PAH-HIV	1	4	1.5	12	19	36	large platelets	4 30"	3 0'	73.9	47.1	dilated	11	N	N	60	TR mild	NO	moderate	3	2	11	19	35	70.5	45	DILATED	11	N	N	60	TR MIL	NO	MODERATE	
104	35	F	75880	LV DAS DYFN	2	4	1.45	11	16	27	LARGE PL	3 0"	3 30"	64	41	RESTRICTED	17	N	+	55	NORMA	PE	MODERATE	3	1.8	10.7	15	27	60.84	39.11	RESTRICTED	17	N	+	55	NORMA	PE+	MILD	